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MEDICINE—A LIFELONG STUDY

Raymond B. Allen, M.D., Los Angeles

I AM proud to have the honor of welcoming you to this great conference on medical education and of saluting you for your dedication to the profession of medicine and to medical education. Ours is a great international fraternity of men and women devoted to the health, welfare, and happiness of people everywhere. Medical education attracts idealistic members of the profession who are concerned about the transmission of the science and the art of the practice of medicine. They cherish the great and rapidly increasing body of knowledge and skills of medicine. They transmit all of this to the young and inculcate in them the ideals and the spirit of service which imbue our great profession.

And so may I express your gratitude and mine to the World Medical Association, its officers and council, for organizing and planning this Second World Conference on Medical Education. That such a conference would be held was inevitable, after the great success of the First World Conference in London in 1953. The impact of the proceedings of that meeting on undergraduate medical education is well known. The success of this one is assured by the meticulous planning of the program committee, and by the distinguished group of leaders in medical educational thought and practice assembled here. You have come from the great medical centers of the world to exchange experiences and ideas about the art of educating and training the physician. Modern technology, it is true, is shrinking distances and making peoples everywhere close neighbors. Even so, your presence here represents sacrifices from your obligations at home, and your colleagues here in America are most grateful for the time you will be spending among us. We do hope that while you are in our country you will spend more than this week with us and visit far and wide.

All of us are indebted, as well, to the World Health Organization, the Council for International Organizations of Medical Sciences, the International Association of Universities, our host organizations, the American Medical Association, and the Association of American Medical Colleges, and to many foundations, corporations, and associations, as well as to individuals who have helped to make our meeting possible.

We are proud indeed that the President of the United States has honored the conference with his sponsorship.

If you will permit this personal note, may I say that as I have worked with Dr. Louis Bauer, a most distinguished physician and the Secretary General of the World Medical Association, I have appreciated his great skill as an organizer and leader. He is learned, humble, sensitive, wise, and, at the same time, decisive (as those of you who have attended meetings of the World Medical Association know full well). His selfless dedication to the best interests of mankind through our profession and medical education is an inspiration to us all.

Chancellor, University of California at Los Angeles.
President's address to the First Plenary Session of the Second World Conference on Medical Education, Chicago, Aug. 31, 1959.

We are here to think together about the problems of medical education and learning which continue throughout the professional lifetime of the physician. Our concern will be with the ways in which the physician may best and most expeditiously extend his knowledge and improve his skills; with the health problems of the community of which he is such an important part; and with the preparation of medical teachers and research scientists.

The Present Challenge

Never, perhaps, has a conference been convened at a time of greater ferment. Perhaps it is not too much to say that this is a period of crisis. I refer to the crisis of the adaptation of science and technology to the problems of the revolution of rising expectations of people everywhere. Information on the advances in science and technology is known world-wide, almost as soon as they occur. Never has a challenge been more immediate; never has the demand for the benefits of science and technology been greater; and never have the problems of medical education and medical service been more urgent. Thus, we meet at a time when our deliberations are world news and our findings and recommendations are eagerly awaited—awaited not merely by our colleagues at home in the profession but by peoples generally and by their governments.

Governments everywhere, and in whatever form, are increasingly aware of their responsibilities to their people. Edmund Burke emphasized this relationship in eloquent words that are meaningful today, when he said:

> Society is indeed a contract. . . . But the state ought not to be considered as nothing better than a partnership . . . . to be taken up for a little temporary interest, and to be dissolved by the fancy of the parties . . . . it is a partnership in all science; a partnership in every virtue, and in all perfection. And as the ends of such a partnership cannot be obtained in many generations, it becomes a partnership not only between those who are living, but between those who are living, those who are dead, and those who are to be born.

It is not my purpose to discuss government in relation to the problems of medical care. This is not the subject of our conference. May I say, however, that to the extent that governments impose regulations on the medical profession that interfere with personal professional service, and regulate medical education in the interest of the political institutions of government, to this extent, the freedom of the individual doctor and professor is impaired. At the same time, medical men have come to appreciate that there are many things which the state can do more effectively in certain aspects of preventive medicine, public health, and medical service. Governments everywhere are in the business of providing hospital services, for example, and this is as true in the United States as elsewhere. The great problems of the mentally ill, of infectious disease and tuberculosis, of mounting populations and of food and nutrition, and of medical services for the armed forces and veterans require community and state action. Without this community contribution of facilities and services, the individual physician and the profession as a whole could not render their most effective service. In a sense, the state with the cooperation of physicians deals with broad environmental problems and organizes facilities within which the profession can provide its independent and essential professional services. Accepted, too, is the fact that the state must exercise a licensing function of physicians and health service personnel. The state, together with the universities and medical schools, guarantees to the public that the medical graduate is qualified to practice medicine, assuming personal responsibility for the health of the individual.

But the medical profession, this conference of the World Medical Association, our national and local associations, and the individual physician himself must be constantly alert lest the independence of the practicing physician or health officer be restricted in his relationship with his patients. The fact that we meet in national and international conferences, publish papers, and communicate with one another on these vital questions without interference by government augurs well for the future and the solution of the problems we will be considering. As long as we, as individuals, are aware of our responsibilities and exercise them with judgment and humility, seeking only the welfare of our fellow human beings, we have nothing to fear for the future of our profession.

Demand for More Service

There are problems, of course, and one of them about which we will be talking is the demand for more medical service, particularly among peoples where facilities are inadequate for training physicians and health personnel in sufficient numbers to meet the needs of the community. Even in the United States, where there is one physician for every 750 people, a recent report to the Secretary of Health, Education, and Welfare indicated that a minimum of 14 new medical schools should be built by 1970 to meet the requirements of medical service to a growing population and expanding economy.

I learned in Indonesia recently that over the next 10 years the number of graduates will be greatly increased and that one physician to 10,000 people, with auxiliary personnel, will be able to meet the health needs of the country. The cooperation of international technical assistance agencies with the universities of Indonesia in this program is an example of world-wide efforts to meet the health service needs of people.

I am convinced that this conference and cooperating governments and organizations can mobilize a tremendous reserve of resources to meet the rising expectations for a healthful, decent existence.

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The international health year presently being proposed will be a year of massive mobilization of all organizations toward these high goals. We will cooperate fully with officers of government, officers of the World Health Organization and the United Nations, and will bend our own individual efforts toward doing what we see in front of us to do, whatever the sacrifice.

More than 30 years ago, one physician made up his mind that he could best serve his fellow men by leaving his honored place in Europe where he was esteemed as a theologian, composer, philosopher, and author and by establishing a modest hospital in the jungle village of Lambaréné in French Equatorial Africa. He still labors there with help from his many friends and admirers around the world to bring modern medicine to the people he serves. I like to tell my friends in this country that he, Albert Schweitzer, was a pioneer international cooperation administrator, and an ornament of our profession. There are many Albert Schweitzers of medicine. In your own way, each of you is practicing this same faith, faith in the individual and faith in yourself and your God.

As we learn to respect ourselves, we learn to respect all life, and especially human life. Out of disregard for human life has grown the crisis and struggle of our times. Unhappily, many people seek only to gratify their own selfish acquisitive instincts. What a tragedy this is when there is enough for everyone's need, but, as someone has remarked, not enough for everyone's greed. The physician, like the philosopher and the saint, puts down this sorry scheme of things as man's baser nature and with patience, kindliness, and tolerance goes about his work of healing, and prays that time will not run out.

As we look back across the cataclysmic years of man's struggle and despair, we are challenged to see to it that centuries hence man will look back and say of us that we built upon the best that was in us and fashioned a better world for them. Medicine, with its age-old concern for the sick, the poor as well as the rich, the weak as well as the strong, has been an influence for good, surpassed only by the moral precepts of religion. The services of medicine, like those of religion, are and will continue to be largely personal. However, medicine must progress as a social as well as a biological science, and must broaden its outlook accordingly.

The timeless quest of medicine is health—health not merely of the individual but of the society that embraces him. Medicine has learned that these goals are actually one and inseparable. Healthy individuals in a healthy society are interdependent for their security and well-being. Unhealthiness in one leads to unhealthiness in the others. The quest of health is timeless, but with ever-changing frontiers. The outcome of the search depends on the imagination, energy, skills, and courage of individuals, and especially of university and medical school men, men of hope and forward-looking mind.

Medicine and Education

Now may I say a word about the relation of medicine to the university as a whole and to education in general. All of us have seen patients who are sick yet have no evidence of organic disease. We have seen sickness of the spirit of man, sickness of the soul. We have seen patients who are sick because they have given up the battle, because they were incapable of dealing with the problems confronting them. But it is rare, indeed, that we have seen a sickness of spirit in a man who has prepared himself well for the kind of world in which he is living. The tragic pity is that many people never have the opportunity to prepare themselves to cope with the problems of the kind of a world which is now emerging—a world of science, technology, and industry—and so we see many neuroses, many psychosomatic disorders for which the cure is difficult because reeducation is difficult, especially when there has been little education to begin with.

An important element in the revolution of rising expectations is the expectation of every parent that his children will have the advantages of an education. It is clear enough to even the lowliest of men that, if his children are to progress and have a better life in an age of science and technology, they must have all the education and training possible. The curiosity, imagination, and great energies of the young need only to be provided with a healthy outlet—serious study, work, and activity, mental, physical, and spiritual, which lead them on to better appreciation of themselves, hopefully to full self-realization. Thus, the young learn that disciplined, well-schooled intelligence is the way to excellence and that through excellence comes self-realization and understanding of themselves and their fellow men. In this manner they grow to maturity and to leadership in a world which will belong to those who are prepared to manage it.

Education and health are inseparably bound together, for unless the mind is trained to think, to create, to work, to try and fail and try again to achieve, nothing results but a boring routine with no self-realization and no real happiness. Happiness is found only in self-realization and it is through the mind, nourished by the healthy food of great ideas, great works, and great achievements of mind, hand, and spirit, that the individual comes to understand and realize himself—who he is and what he can do. This, I suggest, is the binding relation of medicine and education, not merely education of the doctor but education of men.

The physician humanizes science. He brings to science human understanding and warmth, drawing from the rich traditions of his noble

art from all the ages and races of men. Selfless, dedicated, wise, and strong, his is a profession which seeks to embrace the wisdom of the race, the wisdom of the sciences, and the arts in the service of human kind. The physician of the future is our sacred trust. He will cushion the hammer blows of cold science and technology and of powerful government and will help bring to this age peace and good will among men everywhere.

In this conference, ladies and gentlemen, we rededicate ourselves to this great mission of education, joining hands with men of good will in every profession and in government to make a great crusade for the health and welfare of every living soul on this planet. In spite of the many divergent forms of government in the world and of tensions and differences among governments, this bond among men and peoples, though sometimes strained and bent, is never broken.

PROCEEDINGS OF FIRST WORLD CONFERENCE ON MEDICAL EDUCATION

William M. Arnott, M.D., Birmingham, England

"Medicine today demands much from character, intellect and practical ability and medicine also provides a wide variety of opportunity for all kinds of talent. But talents will be wasted or misused if the structure and content of medical education are faulty and if medical educationists remain complacently satisfied with themselves and their methods." With these apt words Sir Lionel Whitby concluded his presidential address to the First World Conference at London in 1953. It is with a deep sense of humility and sorrow that I stand before you, because I know that but for his untimely death Sir Lionel would be in my place and I would not have lost a kind friend and you an inspiring leader.

By a happy inspiration Sir Richard Livingstone, a former president of Corpus Christi College, Oxford, in an address to the opening plenary session struck the keynote of the whole conference when he expounded the philosophy of the first rate in the sense that the hallmark of the educated man is that he knows what is first rate and "that the best educated man is he who knows the first rate in the most important human activities." If the development of such critical appreciation of the first rate in medicine is the objective of undergraduate education, surely the theme of this Second World Conference devoted to graduate education must be the maintenance and sharpening of the same faculty throughout professional life.

The first conference was attended by over 600 men and women representing 127 faculties and 62 countries. Apart from the plenary sessions 87 papers were delivered and the published proceedings amount to 800 pages containing just short of half a million words.

William Withering Professor of Medicine, University of Birmingham.
Address to the First Plenary Session of the Second World Conference on Medical Education, Chicago, Aug. 31, 1959.

The work of the conference was divided into four sections: A, requirements for entry into medical schools, Dr. Victor Johnson, chairman, Dr. Raymond Whitehead, *rapporteur;* B, aims and content of the medical curriculum, Sir Arcot Mudaliar, chairman, Dr. Morgan Jones, *rapporteur;* C, techniques and methods of medical education, Prof. Alberto Hurtado, chairman, Prof. Ian Aird, *rapporteur;* and D, preventive and social medicine, Prof. A. Stampar, chairman, Dr. Charles Fletcher, *rapporteur.*

Requirements for Entry into Medical Schools

The first group of papers were concerned with the general educational background of the prospective medical student. While everybody agreed that this background should be broad there soon emerged the usual controversy as to the part which should be played by the classical tradition based on Greco-Roman studies, philosophy, and history on the one hand, and by a scientific foundation with emphasis on mathematics, physics, chemistry, and biology on the other. The one fact that soon emerged was that an educational program which would reconcile all these varied views would occupy the average student far into adult life and, at best, would leave him fit only to compete in a general knowledge quiz on television and, at worst, would make him completely refractory to all further educational stimulus. Although perhaps not expressed in so many words there was a general realization that the business of doctoring had in it such a large content of chemistry, physics, and biology, much of it quantitative, that for most students a substantial foundation of these subjects had to be laid at the high school or *Gymnasium* level. At the same time, while such might be the path of the majority, provision should be made for the acceptance for medicine of a minority who had shown brilliance in purely classical studies. The

innate ability of these persons would enable them to acquire quickly the necessary grounding in science subjects and to overtake the generality. It was pointed out that the inculcation of a cultural background was not the exclusive perquisite of classical studies but that, properly taught, science could be an intensely humanizing experience as well as a basis for sound doctoring.

Considerable time was devoted to considering the criteria for selection of medical students. It emerged that in some countries devotion to the principle of "the equality of man" excluded any discrimination whatever. All who bore the prescribed educational hallmark were admitted. This practice results in enormous classes in the early years with a very high failure rate. All this leads inevitably to serious impairment of teaching efficiency during the early years with loss of time and frustration of those who are rejected. Although meant to be kind, this indiscriminate egalitarianism can be cruel.

At the same time, while the majority were clearly against mass acceptance there was considerable divergence of opinion as to how best to effect a satisfactory selection. It did seem clear, however, that, while a high standard of performance in the subjects of general education was a useful guide, a careful and skillfully conducted interview was a great help in assessing the important qualities of bearing and character. Contrasting opinions were expressed on the value of psychological tests, although it was, I think, widely agreed that these procedures would become valuable with constant use and systematic correlation of performance with prediction.

It was, obviously, an advantage to be able to select on the basis of individual worth alone without consideration of the extent to which the applicant's family was able to contribute financial support.

In summing up, Dr. Whitehead made a very eloquent plea that we all remember that students were merely ourselves when young and not to expect too much of them. Prof. Samson Wright was quoted as having whimsically described the ideal medical student as "tall, handsome, of great personal integrity, beautifully mannered, cultured, highly intelligent, a tireless worker, original, good with his hands, skillful in exposition, a good mixer, athletic, devoting his spare time to extramural activities, with a good family background, and so on and so forth," a dazzling Olympian but certainly not to be found amongst men.

Aims and Content of the Medical Curriculum

In the section on aims and content of the medical curriculum many speakers emphasized the importance of the university ideal in which emphasis is not on training and instruction in the sense of didactic teaching but to help the student to acquire outlooks and habits of scholarship, to develop his critical faculties to the utmost, and, above all, to be fired with curiosity to know, to find out, and to add to the total of human knowledge.

There was widespread acceptance of the concept that the duty of the medical school was not to produce a general practitioner any more than a surgeon or a hygienist, etc., but the much simpler and more attainable one of advancing the education of the doctor to the point from which he can, within a reasonable period, be turned into a useful general practitioner or, if he be possessed of the required industry, enthusiasm, or ability, can aspire to one or other of the more exacting specialties for which a period of approximately 10 years' postgraduate training is required. Thus, formal qualification is merely the end of the beginning, not an end in itself.

There was frequent use of the blessed word "integration," by which was clearly meant the presentation of a single corpus of knowledge concerned with the health of man. The conventional divisions of medical science into anatomy, physiology, pathology, etc., are to some extent accidents of evolution rather than fundamental in nature, while the subdivisions of clinical practice depend more on historical trends, technical skills, and circumstances of the market place rather than on basic belief.

The importance of introducing an appreciation of statistical mathematics at an early stage was emphasized. It is necessary not that the student become proficient in the arithmetic calisthenics of statistics but rather that he develop a sound philosophy of numerical data. All medical men should have some idea of when data can be usefully compared, the magnitude of error in observation, of the significance of differences, and, above all, that significant numerical correlation does not necessarily imply causal relationship. A doctor must also be familiar with the conventional methods of expressing vital statistics. Much of the opposition to statistics in medicine springs from its power to unmask the falsehood which underlies the careless observation, muddled thinking, and pompous assertion which still bulk so largely in current belief.

A very interesting communication dealt with the teaching of medicine and surgery as a single discipline. This has, obviously, much to commend it, and a useful preliminary to this, which works well in my own hospital, is the retention in medical wards of patients in whom surgical treatment becomes necessary. This brings together easily and naturally surgeons and physicians to their great mutual advantage, and the student does not fall into the error of thinking that there is surgical dyspepsia as distinct from medical dyspepsia or that the physician and surgeon are rivals for, not partners in, the care of such disorders as thyrotoxicosis.

Many speakers expressed the view that topographical anatomy was overemphasized and that undue devotion to dissecting the whole body was

undesirable. Anatomists and physiologists presented stimulating accounts of how they had attempted with considerable success to combine the presentation of their subjects and to link them closely with clinical practice.

Expressed broadly and yet succinctly, it seemed to me that section B considered that the aim of the curriculum was to lay a secure foundation of critical knowledge of human biology and on this to build a concept of clinical practice as an applied science. Parallel with this must go the development of the no less essential qualities of compassion and selfless devotion to the sick—ethics which cannot be taught by precept but only by the example of those devoted to these ideals.

Techniques and Methods of Medical Education

Much of the work of the section on techniques and methods of medical education was inevitably and quite properly a more detailed consideration of the broad aims outlined in section B. The great value of this became apparent at the final plenary session and is fully realized when one studies the proceedings. There was a highly diverting and somewhat controversial discussion on the place of the strictly whole-time clinical teacher. It was clear that in this problem much depended on the national background. In Britain, where a very high proportion of patients are treated in state hospitals and in which whole-time as well as part-time teachers enjoy similar facilities, deal with the same social range of patients, and, to some extent, see patients in their homes (without, of course, receiving a fee personally), the distinction between the two categories has become virtually insignificant. It was, however, widely agreed that the student should be taught by both varieties of teacher, indeed that each was complementary to the other. Personally, I am in the strongest possible agreement with this viewpoint.

The systematic lecture came in for some heavy criticism. Didactic rather than Socratic teaching, large classes, crowded ward rounds, overemphasis on theoretical lectures, lack of contact between staff and students, excessive reliance on textbooks, and examinations which test memory more than reasoning are all to be avoided in education for medicine. There seemed little doubt that most people appreciated the importance of clinical education by practice and example. The incorporation of the student into the team concerned with patient care and his presence throughout the vicissitudes of a wide variety of incidents of illness is of prime importance.

Claims were made for teaching in the policlinic, in the home, in the laboratory, etc., but I gathered the impression that any place was suitable provided the teachers were keen and capable and that they were dealing with real live problems of health and disease. The opinion was expressed that the extent to which the various specialties of clinical practice and types of disease was emphasized in the curriculum should bear a quantitative relation to the frequency with which they were encountered in daily life. This was countered, and I think rightly so, by the opinion that subjects should have a degree of importance attached to them dependent on their scientific sophistication. Thus emphasis on cardiovascular disease and neurology would rightly be educationally advantageous.

Preventive and Social Medicine

In many ways the liveliest and most productive section of the conference was that on preventive and social medicine. A perusal of the record leaves no doubt that good doctoring entails a proper appreciation of the environment in relation to health and disease. The many excellent papers effectively dispelled any lingering doubts as to any undesirable political implication of the term "social medicine" while at the same time making it abundantly clear that the effective promotion of health, and the adequate provision of medical and material aid for the sick and their families, is an essential feature of any well-ordered community. Whether this be provided by the state or by efficient private enterprise seems largely irrelevant, and a matter that can be left to the inclinations of each nation. The essential thing is that it shall be provided. It was emphasized that, while the principles of preventive and social medicine should imbue all clinical teaching, these subjects constituted academic disciplines in their own right and that a medical school needs specialists in the various aspects of the subject.

Conclusions

You will realize that because of my own inadequacy and the strict limitation of time necessarily imposed on me this is a ludicrously inadequate survey of the first conference. I have been viewing it at a reduction factor of approximately one in 250 with an optical system which visualized only what I wanted to see, but which I hope is free from chromatic aberration.

In conclusion, I wish to emphasize one consideration which seems to me of paramount importance in the lifelong study of medicine and which was implicit in much of the work of the first conference. The lifelong maintenance of a high standard of informed, critical and conscientious practice depends more than anything else on the avoidance of professional isolation. Where doctors are continuously subject to the kindly mutual criticism and approbation of their peers it becomes difficult for them to allow their standards to slip and their minds to crystallize. The circumstance that teaching hospitals are, in general, the best hospitals, that medical teachers constitute in the main the leaders of our profession is due not only to careful initial selection but to the fact that the teachers work constantly in the fierce light of the critical appraisal of their colleagues and even more so of their students. Whether they like it or not they are set on a pedes-

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tal which can so easily become a pillory. I hope, therefore, that full attention will be paid to the promotion of professional association, which is much more important than formal refresher courses. This is particularly important for family doctors. I hope also that we will face squarely the fact that it can easily happen that a system of remuneration can minimize such association by tending to make practitioners commercial rivals rather than professional brethren. Where such occurs everything possible must be done to overcome such influence.

The widely scattered doctors of the less well-developed territories are also a problem. It so happens that in the last two years I have traveled nearly 40,000 miles in three long medical tours in British Africa, mostly equatorial Africa, so that I might learn something of the outlook of doctors there and perhaps give them something of my outlook. The circumstances of these lands present formidable difficulties, but I will close by quoting the motto of my University of Birmingham: *Per ardua ad alta.*

RESULTS OF FIRST WORLD CONFERENCE ON MEDICAL EDUCATION

Ian Aird, Ch.M., F.R.C.S., F.R.C.S.E., London

I have distributed questionnaires to the 400 medical teachers who attended the First World Conference on Medical Education and received about 100 answers. About 20 correspondents replied that they had learned nothing new at the conference and that the conference had consequently had no effect on their teaching methods or on the medical curriculum in their medical schools.

The great majority of the answers, however, expressed strong appreciation of the conference itself, and the value of the opportunity of informal conversation with delegates from other medical schools and other countries was frequently stressed. A majority of those answering could not single out any particular alteration in the method of teaching or in the content of the medical course, but they believed that the conference was responsible for a freshening revival of educational ideals. Most delegates seem to have been stimulated to renew their own positive thinking about educational aims and methods.

On the positive side, it is clear that the published proceedings of the first conference were of great value to those responsible for new medical schools that have been brought to birth in the last few years. Delegates from six important countries have been able to report that the proceedings have been closely studied by the authorities responsible for drawing up the curriculums in new universities. In two other countries, Germany and Chile, the curriculum of medical schools has been recently reviewed and the delegates from these countries to the conference have reported that due and detailed consideration was given by the replanning authorities to the proceedings of the first world conference. In Britain the General Medical Council has recently brought forward recommendations for improvement in the curriculums of medical schools, and a study of these recommendations shows that many ideas expressed in these recommendations are in close parallel with deliberations at the first world conference. It seems clear that the proceedings of the first world conference are likely for some considerable time to exercise an important influence on the intellectual architects of new medical schools.

In general the ancient medical schools of wealthier, more highly industrialized countries have been disinclined to alter their established curriculums and teaching methods. Delegates from these medical schools reporting their conservatism have reacted to the conservatism in different ways. Some of the delegates have been convinced by the conference that the methods of their own schools cannot be bettered, and in a great many instances one is forced to concur with this view. Some other delegates from such schools, however, have returned home after the conference with a fervid ambition to make important alterations in teaching programs and methods but have failed to enlist the support of those colleagues who had not attended the conference. It seems probable that the conference, in fact, attracted men who already felt that the medical course in their own schools, as in other schools, was still imperfect.

The conference seems to have been most appreciated by delegates from less wealthy and less highly industrialized countries, and the effect of the conference seems to have been greatest in the medical schools of these countries. Even so, however, delegates from these countries are those who in writing to me have shown the greatest frustration. Returning to their countries imbued with new ideas from the conference they have been balked in their ambitions and in their enthusiasm by the poverty of their countries' educational budgets. A striking

Professor of Surgery, University of London, Director of Surgical Studies, Postgraduate Medical School of London.

Read before the Second World Conference on Medical Education, Chicago, Aug. 31, 1959.

antithesis has emerged in this correspondence between the inertia of intellectual self-satisfaction that has assailed delegates returning from the first conference to old medical schools in highly industrialized countries, and the economic inertia which has balked candidates returning to less highly industrialized countries.

Frequent praise is directed, however, to the success which the conference had in a restatement of the aims and ideals of medical education, and it is clear that most delegates returned spiritually refreshed by the conference.

Effect on Curriculums

Some delegates took back to their universities the agreement of the conference that, in a consideration of requirements for entry, due weight should be attached to a broad general education and adequate consideration should be given for some knowledge of such liberal subjects as Greek, Latin, history, philosophy, the arts and music, tempered by the opinion of the conference that science was not inferior to the humanities as an educational exercise. The conference can perhaps hardly take credit for the decision of Oxford and Cambridge to remove Latin from the compulsory entrance subjects, but certainly it is only since the conference that this measure of educational freedom has been instituted. It appears that as a direct result of the conference some medical schools have adopted new educational devices for assessing the character and intelligence of entrants to the medical profession.

With respect to the aim and content of the curriculum, Sir Richard Livingstone's advice that our aim be a "basic doctor with the philosophy of the first rate" has made a striking impact on most delegates and it must have echoed and reechoed literally hundreds of times during these last five years in university planning committees all over the world. In this field striking results have in fact been reported, and the delegates from a majority of medical schools report improvements or at least changes, though only a minority ascribe these changes directly to the conference.

Anatomy and physiology have in many places been integrated, though in some newer universities in less industrialized countries there is a lack of teachers in these subjects. An introductory or basic course of clinical medicine has been very widely introduced, sometimes by the direct machinations of a delegate to the conference, and in a good many places surgery and medicine have been integrated with anatomy, physiology, pharmacology and pathology. A few schools have actually managed to call a halt to expansion of the curriculum and some show a new restraint in the teaching of the narrower specialties.

Psychological medicine is in some places now covered by a broad general course, with the implied recognition that clinicians in their general teaching of medicine and surgery must accept responsibility for instruction in psychological aspects of their clinical work. In a good many countries the teaching of detailed obstetrics is contracted with a compulsory increase in the teaching of antenatal and postnatal care.

The conference attracted additional publicity, if that were possible, to the important experiment at Western Reserve, and that medical school must have been embarrassed by the number of visitors which their conference delegates attracted. One of the refreshing results of the conference which is unmistakably on the positive side is the international visiting which has resulted from new acquaintances made in London five years ago.

The section on technique and methods has come in for a good deal of praise and some criticism. The practice of reducing attendance of students in operating theaters to an absolute minimum has become much wider since the first conference. In many places the medical students now visit patients in their own homes. Polyclinics for the use of students in outpatient departments have proved to be very popular, and the Singapore experiment of providing laboratories, roentgenologic equipment, endoscopic facilities, and electrography in the polyclinic has been followed in some other places. Reactions to the various lectures and demonstrations on visual aids have been less uniformly popular. Expense seems here to have prevented ideals from being attained.

Index of Medical Films

I have explored the suggestion made at the first conference that a central museum, based on the Wellcome principle, should be established for the collection and distribution of demonstration material, but this seems to be quite impracticable. More possible is the preparation of an index of medical films. Dr. J. M. Mackintosh of the World Health Organization has given me advice in this matter. He informs me that the preparation of an index of these films would offer the greatest possible difficulties. Thousands of medical films exist of a quality varying from excellent to useless. At a recent conference on accidents in the home over 50 films were produced on this subject alone and a WHO seminar had the greatest difficulty in distinguishing the good from the bad. There are also many lists of films extant, none of them complete, few of them evaluated, and most of them out of date. It seems probable that only a limited scheme could be attempted with any prospect of success. Some countries already have a centralized film service such as the Medical Committee of the British Scientific Film Association, the British Medical Association, the British Council, the Canadian government, and the American College of Surgeons, and the Film Reference Guide for Medicine and Allied Sciences of the U. S. P. H. S. A multiple index comprising the individual indexes of such organizations, kept fully up to date and strictly selective by high level national appraisal, would seem easily possible and might be very profitable.

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In many centers the data produced at the first conference on medical school libraries have been responsible for local improvements. The report that in the United States medical school libraries varied between 3,000 and 375,000 volumes shows how much still remains to be done in this field. As a result of the conference, a good many medical centers are now giving their students instruction in the use of the library.

No one seems to have changed his view, whatever that was before the conference, about the superiority of the internal or the external examination, but multiple question examinations have been brought into use much more widely than I, for one, would have imagined.

Little has been reported by my correspondents on changes in the teaching of preventive and social medicine, but several medical schools have recognized now as a result of the first conference that special departments are necessary for the teaching of these subjects. Note has been taken widely of the need for the student to realize the importance of a full industrial history and in one center tape recordings of social interviews have been introduced for student instruction. In a few places students have been encouraged to undertake family supervision.

Conclusions

It would thus appear that there have been wide repercussions from the first world conference even though some persons have been disappointed, only a few of them in the conference itself, many of them in what they have been able to achieve as a result of the conference by direct action in their own medical schools. The conference does, however, seem to have more than justified the communal expense and time expended. It should be said at the start of this conference that many of my correspondents expressed some dissatisfaction at the actual form which the first conference took. Many were disappointed that the greater part of the time was taken up by the delivery of previously prepared papers. They would have preferred open discussion possibly by panel groups and a less rigid presentation of unrelated or repetitive facts and opinions.

I must express my gratitude for the trouble so many busy medical teachers have taken in replying to my inquiries. I hope my correspondents will accept this deep expression of acknowledgment and gratitude.

Hammersmith Hospital, Ducane Road.

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INTERNATIONAL COOPERATION IN POSTGRADUATE MEDICAL EDUCATION—CROSS-FERTILIZATION OF IDEAS

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It would be impossible and perhaps superfluous to attempt to review in a brief statement all the efforts and methods applied internationally in relation to what some call "post-basic" medical education. Therefore, I shall limit my remarks to a few more general aspects of the subject.

The desire to share with others the benefits of advanced knowledge was characteristic of all truly great civilizations. Indeed many famous centers of science in the East and the West alike, at the time of their flourishing, spread medical knowledge far beyond the boundaries of their countries. Because of its multiple roots, its goals and its applicability, medicine is with good reason looked upon as an international science and a part of a world-wide civilization.

Outstanding medical achievements sometimes place one or another nation ahead of the others and make such a nation the example and the teacher. So far in history such a leading position usually has been rather limited in duration and scope; no single center, no single country—no matter how powerful—has been able to rely exclusively on its own resources and stimuli for any length of time.

International cooperation in advanced, i. e., postgraduate and graduate, medical education has mainly two aspects: (1) training abroad at a level, or regarding a type of knowledge, not available at home and (2) keeping abreast of medical progress achieved elsewhere.

A large number of forms and methods have been tried out, applied, and developed in this area by various agencies and institutions working in collaborative activities. For instance, the WHO in its program uses (1) fellowships and travel grants for studies abroad, (2) visiting professors for short and long assignments, (3) visiting teams of medical scientists, (4) consultants on educational matters, (5) exchange of teaching and research staff, (6) international courses and seminars, (7) support to conferences on medical education and world-wide, national, or regional meetings, and (8) studies of selected educational subjects.

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Read before the Second World Conference on Medical Education, Chicago, Aug. 31, 1959.

Aspects of Foreign Medical Training

In relation to training abroad, it is interesting to observe that, in spite of the various financial, administrative, and linguistic barriers, about 20,000 medical people studied abroad in each of the last few years and over 2,000 institutions accepted foreign postgraduate students. In recent years a higher proportion of these studies has been sponsored by official agencies in comparison with the early part of the century, when much study-travel was personally arranged by the interested individuals. We can also note a gradual increase in educational travel sponsored by international agencies. In several countries special arrangements have been made in order to meet the growing programs for foreign physicians and to facilitate access to host institutions. In some of them, the programs sometimes go beyond the walls of the host institution and include extramural aspects of the problem studied.

This point deserves some elaboration. In almost all countries great advances in health could be achieved through medical and related measures right now if the already available knowledge were put into action properly and on an adequate scale. Therefore, acquaintance with methods of practical and massive application of medical progress is often equally as important to foreign students as is the acquiring of the scientific substance itself.

Anyone who is acquainted with the problem knows how often postgraduate students from many countries have been frustrated on their return home because of the difficulties they encountered when they tried to apply their new knowledge in their own local conditions. The stronger ones among them attempted to change the conditions—not always with success—but many became discouraged and limited their struggle to their immediate personal problems. How often the latter return from foreign study acquainted with only one organizational pattern of medicine, of medical research, or of their own specialty! They are naturally bound to imitate the only pattern they know and could be easily criticized at home for imposition of a foreign model unsuitable for the local conditions. Studies in more than one country can improve the situation but the problem should really be tackled from the other end, i. e., finding out the proper ways to advance the matter in the country itself. A great task emerges of making education abroad meet the real needs not only of the students themselves but also of their nations. This in turn requires much more knowledge of the various ecological and health conditions in all corners of the world.

In addition to the well-recognized, time honored objectives to improve the individual's knowledge and technique and to stimulate research and teaching in the home countries of students, international cooperation should put great emphasis on the search for talented persons, who, because of lack of adequate conditions in their own country, cannot develop to their best and thus remain lost to their nation and to medicine.

Another aspect of training abroad needs to be strongly reflected in the programs, i. e., preparation for the functions of leadership in the student's own specialty. Whereas upon completing their training the national trainees usually expect to find a clearly defined place in an organized structure under the guidance of more senior leaders, the foreign trainees quite often will be the only advanced specialists in their city or their country. They will have to do the pioneering work and create the working conditions for themselves and their juniors. Although it is true that good persons make good institutions, the complexity of modern medicine requires well-organized machinery at its every step from research to practical massive application. Some knowledge about these matters should be acquired at some stage of all the types of programs we are considering here.

Technical skills, scientific methodology, and acquaintance with the modern equipment are but a part of the benefit of the training abroad. This should be supplemented by inspiration with medical and scientific ideals, social usefulness of medicine, and knowledge of effective organization of work. With all due respect to the spontaneous growth of national experience in these matters, the potentialities of international cross-fertilization of ideas should not be overlooked. Indeed, they urgently need further energetic advancement.

In spite of their unprecedented growth, studies abroad still do not meet adequately the needs of all nations. Moreover, the other equally important side of the same problem remains even farther behind the needs and requires even more vigorous strengthening and support. This is bringing the advanced medical knowledge from abroad to the place within each country where it can be usefully absorbed. National centers for advanced education can reach a greater number of doctors than those who can travel abroad. International support is greatly needed for the establishment and operation of such centers, for in several countries national resources can be stimulated and developed, if strengthened from abroad.

In some areas a national center for postgraduate education can serve several neighboring countries and thus became a regional center. In others a cooperative intercountry program can be limited to certain selected subjects. Examples of successful international cooperation of this kind are already available. They should be followed.

Everybody today is convinced of the importance of fundamental research in medicine, and the problem of development of researchers and teachers will receive adequate attention at this conference. Therefore, it will suffice here just to emphasize that international cooperation in this area seems to be particularly indispensable and promising. However,

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medical knowledge finds its complete justification, and indeed its title to glory, when it is fully and widely applied to all people in all nations. Postgraduate educational programs should be conceived with the consideration of this basic aim of medicine in mind.

In spite of some shortcomings, other means of advanced education, such as international scientific and professional meetings and the flow of medical literature between countries, continue to increase in scope and volume. Language difficulties still represent a considerable handicap in communication, but there is still another point of some importance which may be raised in such an international gathering as this conference. Medical literature and other educational media in many countries give relatively more attention to the achievements of their nationals than of foreigners. Except for a number of universally recognized names, medical publications, and particularly textbooks, mention more often the names of those who published in the same language than the names of others. This rather understandable phenomenon presents some problems, as, for instance, when medical progress is attributed to the contributions of the various national or linguistic groups. Attempts have been made in some countries to review medical history so that the contribution of those who worked and published in the less known languages might be duly recognized. This trend to appreciate the "forgotten men," not only of the medical past but also of its present, may well deserve some place in international educational cooperation. I cannot forget an experience in a country exposed to changing cultural influences, where the oldest group of leading medical scientists reflected the influence of German medicine, the middle-aged group reflected French, and the youngest one reflected English and American medicine. The loyalty to their teachers and the literature of the language they knew well made the understanding between the three groups quite difficult.

Some understanding between the natural preponderance toward national source and a broader international perspective may lead to more just and balanced views on the truly multinational sources of medicine, yesterday, today, and tomorrow.

Further exploration and action through international cooperation is needed in postgraduate medical education with particular regard to programs, coordination, languages, and orientation. The following questions might be asked: 1. How to develop further internationally assisted programs best suited to the future responsibilities of postgraduate foreign students and the needs and potentialities of their countries. This should also include international support for the host and home training institutions. 2. How to bring about a sufficient but not too rigid coordination of the various efforts undertaken internationally. 3. How to overcome the language barriers in the flow of medical knowledge, particularly with regard to the less generally used languages. 4. How to preserve, enrich, and make universal the inherent permanent values of medicine, independent from transitory "cultural accretions" and national dominations, which can constructively support any freely developing culture based on science and ethics and thus permeate international educational programs.

The answer to these questions should bring us closer to Descartes' farsighted image of medicine as a constructive guide toward a better and wiser community of men throughout the world.

HENS—EGGS—AND FUNGICIDE-TREATED AND FUMIGATED GRAINS.—Tetramethylthiuram disulfide (TMTD), Arasan, is widely used as a fungicide in the treatment of commercial seed corn. Ethylene dibromide (EDB), Dowfume EB-5, is widely used to fumigate grains stored in commercial elevators and farm granaries for the control of weevils. . . . In 1955, it was reported that feeding corn treated with TMTD to laying hens resulted in the production of soft-shelled and misshapen eggs. . . . Workers in Israel reported that grains fumigated with EDB, when fed to laying hens as part of their ration, resulted in a gradual diminution in egg size and, in extreme cases, to complete cessation of egg production. . . . During 1957, an egg producer in South Carolina, maintaining flocks totaling up to 10,000 birds, complained of a diminution in egg size and number after feeding oats as part of the laying hens' ration. The oats had been treated with the grain fumigant EDB. The birds laid numerous so-called "pee-wee" (less than 18 oz. per dozen) and small (less than 21 oz. per dozen) eggs. The egg size improved when the fumigated oats were withheld, but did not return to normal. . . . Feeding trials [revealed that] corn containing tetramethylthiuram disulfide (TMTD) . . . fed to laying hens may have a disastrous effect on egg production even when such grains are heavily diluted with nontreated corn.—B. W. Bierer, V.M.D., and C. L. Vickers, D.V.M., The Effect on Egg Size and Production, of Fungicide-Treated and Fumigated Grains Fed to Hens, *Journal of the American Veterinary Medical Association*, May 15, 1959.

RELATIONSHIP OF SIALIC ACID AND C-REACTIVE PROTEIN LEVELS IN HUMAN SERUM

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and
Henry Kenkel, M.D., Cincinnati

Total protein-bound sialic acid content was determined in normal and pathological human serum with special reference to the C-reactive protein test. Almost all of the serum positive for C-reactive protein had high sialic acid levels. It is likely that different pathological processes may account for the appearance of C-reactive protein and increase in the serum sialic acid level. Nevertheless, it is believed that determination of the level of serum sialic acid should prove a useful adjunct to the diagnosis of rheumatic fever and related diseases. The C-reactive protein itself did not contain sialic acid.

It is well known that C-reactive protein appears in human serum in certain pathological conditions such as rheumatic fever, myocardial infarction, and acute inflammatory diseases. On the other hand, the serum glycoprotein or seromucoid level also increases in such diseases, and the close relationship between the seromucoid level and results of the C-reactive protein test has been reported by Shetlar and co-workers.[1] In their investigation, however, protein-bound polysaccharide content was measured as an index of seromucoid by the determination of hexoses.

In 1948 Niazi and State[2] found, for the first time, that the intensity of purple color produced by the serum diphenylamine reaction was increased in patients with rheumatic fever and cancer. Recently, Coburn and co-workers[3] reported the relationship between the C-reactive protein finding and the diphenylamine reaction. Neither report, however, translated the results to actual values of the chromogenic substance. In 1955 Odin[4] identified the chromogenic substance in human serum protein as *O*-sialic acid (*N*-acetylneuraminic acid), one of the nonprotein constituents of glycoproteins. Despite increasing recent interest in the distribution of sialic acid in biological materials, the physiological and pathological significance of this substance have not as yet been clarified.

This report is concerned primarily with serum sialic acid determination in human subjects, with special reference to the appearance of C-reactive protein in these same persons. The relationship between the serum sialic acid level and antistreptolysin O titer was also examined.

Materials and Methods

Patient serum sent to the clinical laboratory of St. Mary's Hospital for the determination of C-reactive protein content and antistreptolysin O titer was used for the determination of sialic acid content. The serum sialic acid level was determined according to the method for the serum neuraminic acid determination reported by Böhm and associates.[5] As a standard reference of the chromogen, crystalline *O*-sialic acid which was prepared from bovine submaxillary mucin according to Saito's[6] method was used. The color intensity was measured by the Leitz-Mass photoelectric colorimeter with use of a green filter.

From the Institutum Divi Thomae and St. Mary's Hospital.

The C-reactive protein determination was made by the capillary precipitin method devised by Anderson and McCarty[7] with the use of commercially available C-reactive protein antiserum. The antistreptolysin-O titer was measured by Rantz and Randall's[8] procedure with use of Bacto-streptolysin O reagent.

Results

The results are presented in the table. The mean values of serum sialic acid in healthy serum (15 blood bank samples), serum negative for C-reactive protein, and serum positive for C-reactive protein (suspected pathological samples) were 130 ±6.6, 143 ±7.5, and 259 ±12.4 mg. per deciliter respectively. As seen in the table, the serum of patients with a positive C-reactive protein reaction showed a high sialic acid level. The maximum sialic acid value of serum negative for C-reactive protein was 210 mg. per deciliter (shown in only 3 patients of 24). Only 4 of 34 serums positive for C-reactive protein showed less than 210 mg. per deciliter of sialic acid.

No definite correlation between the C-reactive protein titer and the serum sialic acid level was found, and the serum samples tested were, therefore, classified by positivity of the C-reactive protein test. Similarly, no correlation was found between sialic acid level and antistreptolysin O titer.

Consecutive determinations of the serum sialic acid level and the C-reactive protein titer in the same patient have been done in two patients with

typical rheumatic fever. In one case (fig. 1) the final diagnosis was recurrent rheumatic fever with carditis and the patient was treated with penicillin. In the other case (fig. 2) the final clinical diagnosis was acute rheumatic fever with carditis and mitral insufficiency and the patient was treated with digitalis and penicillin.

Serum Sialic Acid Levels and Antistreptolysin O (ASO) and C-Reactive Protein (CPR) Titers in Fifty-eight Patients

No. of Case	Sialic Acid Level, Mg./Dl.	ASO Titer, Units	CRP Titer, Min. of Precipitation
1	160	50	neg.
2	120	50	neg.
3	120	50	neg.
4	120	50	neg.
5	130	50	neg.
6	130	50	neg.
7	140	100	neg.
8	210	100	neg.
9	140	100	neg.
10	100	125	neg.
11	100	125	neg.
12	210	125	neg.
13	190	166	neg.
14	120	166	neg.
15	140	250	neg.
16	115	333	neg.
17	140	333	neg.
18	140	333	neg.
19	190	500	neg.
20	180	625	neg.
21	210	833+	neg.
22	160	...	neg.
23	110	...	neg.
24	140	...	neg.
25	350	50	1
26	220	166	1
27	260	333	1
28	270	333	1
29	220	500	1
30	340	625	1
31	170	333	1-2
32	180	250	1-2
33	240	50	2
34	340	250	2
35	220	1,250	2
36	240	250	2
37	210	12.5	2-3
38	270	12.5	2
39	220	166	2
40	240	125	2
41	210	250	2
42	200	625	2
43	280	166	3
44	250	333	3
45	150	50	3
46	250	166	3
47	220	166	3
48	260	625	3
49	210	500	3
50	250	625	3
51	240	625	3
52	320	625	3
53	240	625	3
54	480	...	3
55	250	250	4
56	140	50	4
57	420	625	4
58	280	50	5

Comment

As shown in our data, as well as in the results of Coburn and co-workers,[3] there apparently exists a close relationship between the appearance of C-reactive protein and the increase of serum sialic acid level, although in some cases no correlation was found between results of the two tests. But for these cases, the correlation might be suspected to be accounted for by the possible presence of sialic acid in the C-reactive protein itself. This alternative was eliminated by testing the C-reactive protein for sialic acid, with negative results.

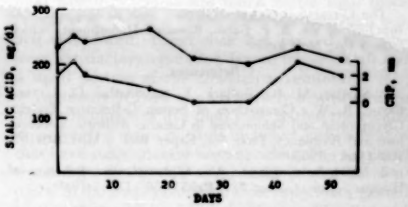

Fig. 1.—Relationship of serum sialic acid levels and C-reactive protein titers in patient with recurrent rheumatic fever with carditis. Closed dot = serum sialic acid level; open dot = C-reactive protein titer.

The reason for the lack of correlation in the several cases mentioned above awaits further investigation. It is likely that different pathological processes may account for the appearance of C-reactive protein and an increase in the serum sialic acid level. Nevertheless, from the data presented, it is our opinion that determination of the level of serum sialic acid should prove a useful adjunct to the diagnosis of rheumatic fever and related diseases.

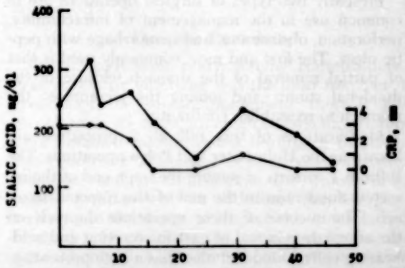

Fig. 2.—Relationship of serum sialic acid levels and C-reactive protein titers in patient with acute rheumatic fever with carditis and mitral insufficiency.

Summary

The total protein-bound sialic acid content was determined in normal and pathological human serum with special reference to the C-reactive protein test. Almost all of the serum positive for C-reactive protein had high sialic acid levels. The

relationship between the serum sialic acid level and the antistreptolysin O titer was examined, and no correlation was found. The C-reactive protein did not contain sialic acid.

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The C-reactive protein antiserum used in this study was supplied by Dr. R. P. Gatto, Research Department, Schieffelin & Co., New York.

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EVALUATION OF VAGOTOMY AND ACCOMPANYING DRAINAGE PROCEDURE

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The operation of vagotomy alone or in combination with other gastric surgery has been carried out in 322 patients. Vagotomy alone was performed in 27 patients with peptic ulcer, but 10 of these required further surgery because of gastric retention. Vagotomy was done with subtotal gastric resection in 29 patients with peptic ulcer, with gastrojejunostomy in 93 patients, with duodenal ulcer, and with pyloroplasty in 162 patients with duodenal ulcer. The choice of operation depended on the patient's history. The explanation of varying postoperative results was therefore difficult, but the probability of good results was significantly higher when the combination of vagotomy and pyloroplasty was used. The operation of pyloroplasty affords the surgeon good visualization of the ulcer area at operation, is more effective in eliminating antral stasis and decreasing regurgitation of jejunal contents into the stomach, and facilitates subsequent operative procedures.

Most patients with peptic ulcer are treated satisfactorily by medical regimen, but recurrences and complications call for surgical intervention. When indicated, operation will accomplish the desired result in a high percentage of cases.

Presently two types of surgical operations are in common use in the management of intractability, perforation, obstruction, and hemorrhage with peptic ulcer. The first and most commonly used is that of partial removal of the stomach, closure of the duodenal stump, and joining the jejunum to the stomach to reestablish continuity.

Modifications of this Billroth 2 procedure are known as the Hofmeister and Polya operations. The Billroth 1 consists of joining the open end of the resected duodenum to the end of the resected stomach. The success of these operations depends on the adequate removal of gastrin-secreting and acid-bearing cells. Duodenal ulcer has a high percentage of recurrence and from this standpoint a resection operation, to be successful, must be thorough and radical to prevent the subsequent appearance of stomal or marginal ulcer.

Another method of surgical treatment, thoroughly investigated experimentally and clinically and introduced by Dragstedt and Owens [1] in 1943, is the division of both vagi at or below the esophageal hiatus. Vagus section was then combined with a procedure to prevent gastric retention, namely, subtotal gastric resection, gastrojejunostomy, or pyloroplasty.

Pathogenesis

On the grounds that antral hyperfunction is the cause of gastric ulcer, one would not expect vagotomy to be the treatment of choice in this problem.

Experimental evidence and clinical experience, however, indicate that antral stasis is the cause of this hyperfunction which results in an excessive secretion of gastric juice through prolonged liberation of gastrin. About 20% of gastric ulcers occur in patients with previous duodenal ulcers, and stasis here is likely to be caused by stenosis at the pylorus. In the remainder, gastric stasis on an atony basis alone accounts for the development of gastric ulcer. A drainage procedure such as gastroenterostomy will, therefore, exert a healing effect on the benign gastric ulcer by relieving gastric stasis, and antral resection is not followed by marginal ulcer. On the other hand, in those patients with benign gastric ulcer in whom a low gastric resection has been done and followed with occurrence of marginal ulcer, it is probable that there is more than simply an increased secretion of gastrin due to antral stasis and that this patient also is secreting a gastric juice, the stimulation for which is of cephalic origin. If night secretion exceeds 20 mEq. of hydrochloric acid in a 12-hour period, the vagotomy combined with antral resection should be performed.[2]

In duodenal ulcer, there is an accompanying increase in gastric secretion. This is particularly appreciated if one considers the hydrochloric acid output in milliequivalents, which is markedly increased above normal with the increase in volume of secretion as well as with the increase in clinical units of free acid as demonstrated in the between meal build-up and overnight gastric secretion in the patient with a duodenal ulcer. The output here is commonly 60 and 70 mEq. of free hydrochloric acid during a 12-hour fasting period, as compared with 10 to 20 mEq. put out by the normal stomach.[2] This hypersecretion characteristic is chiefly, if not entirely, dependent on an exaggerated cephalic stimulation. In vagus section we have an effective method of abolishing this neurogenic phase and, with the decrease in gastric secretion, healing of the duodenal ulcer. In duodenal ulcer the antrum mechanism of secretion is probably normal and removal of the antrum is unnecessary. Removal of the gastric glands is also unnecessary since a reduction of their activity can be accomplished through abolishing the stimulation of their activity. The storage function of the intact stomach may be preserved.[2a]

Complications

The long-term results of treatment are satisfactory in both methods and good results are reported in about 85% of cases, after either adequate partial gastric resection or vagotomy combined with gastrojejunostomy or pyloroplasty. The incidence of stomal ulcer after Billroth 2 gastric resection varies from 2 to 6%. Occurrence of marginal ulcer after subtotal gastric resection is more likely if the operation is done for intractability or for perforation in a patient with a duodenal ulcer. Such complications often occur in the patient who exhibits excessively high volume of secretion and acidity. Marginal ulcer occurring after subtotal gastric resection is much less likely if the resection is done for obstruction or for the benign gastric ulcer.

The results secured today in the best surgical clinics in the treatment of duodenal ulcer by subtotal gastric resection are much better than those obtained in the same hands when the operation was first introduced. Experience has proved that the most satisfactory operation is one in which all but a small portion of the stomach is removed.

Vagotomy in 1946 was a relatively new procedure and technique was in a fluid state so that the results in a reported series of cases included early mistakes that have subsequently been avoided. The results in those days of my own early cases cannot be compared to the results obtained after experience gained in the observation of the various modifications of the actual vagotomy and its accompanying drainage procedure.

The early complications after subtotal gastric resection are obstruction at the anastomosis with gastric retention, leakage of a duodenal stump, infection, and wound disruption. Late complications are postprandial pain, dumping syndrome, marginal or stomal ulcers, and loss of weight.

The early complications after vagotomy and a drainage procedure are gastric retention, postprandial pain, and cardiospasm. The late complications are recurrence of ulcer due to incomplete vagotomy, gastric retention with its symptoms of belching and bloating, dumping syndrome, obstruction due to cicatrization, transient diarrhea, and loss of weight.

The mortality after subtotal gastric resection is reported 1 to 3%, and after vagotomy plus a drainage procedure the mortality is reported to be around 0.5%.

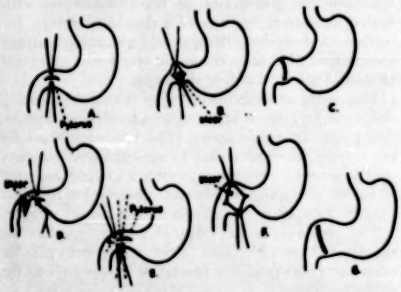
Drainage Procedure

Of the significant postvagotomy complications, delayed gastric emptying was the most frequent. I abandoned the supradiaphragmatic thoracic approach after 25 cases, although satisfactory results were obtained insofar as the healing of the ulcer was concerned. Frequency of postoperative gastric retention, inability to combine the transthoracic vagus operation with an additional drainage procedure, and the desire to inspect the stomach and diseased area all led to the preference for an abdominal operation. The transthoracic vagus section is now confined to use in the instance of marginal ulcer after an original abdominal operation or recurrence of duodenal ulcer with evidence of incomplete vagotomy by previous surgery.

Gastrojejunostomy as the drainage procedure was used in the majority of my cases until 1952 but has been used to a diminishing extent because of the occasional difficulty with emptying and antral stasis. Inflammation of the gastric mucosa from regurgitation of jejunal content, troublesome jejunitis, antral stasis and its stimulation of the secretion of gastrin, technical difficulties resulting in ob-

struction of the afferent loop and its invitation to the possibility of ulceration at the site of anastomosis, and inability to visualize the duodenal lesion or distal construction in the duodenum have to a degree been overcome by a more distally placed smaller gastrojejunostomy on the most dependent portion of the greater curvature.

The use of pyloroplasty as the drainage procedure eliminates the danger of stasis in a redundant antrum and decreases the incidence of other objectionable features above mentioned. A simple pyloroplasty does not alter the normal continuity of the gastrointestinal tract, eliminates the possibility of jejunal ulceration, and carries a low surgical morbidity. If a subsequent gastric operation should become necessary, this can be performed more easily after a previous pyloroplasty than after a gastrojejunostomy or subtotal gastric resection. A pyloroplasty allows for the inspection of the mucosa of the affected area, and this may be especially im-



A, gastroduodenostomy incision, 6-8 cm., placement of guy sutures; B, demonstration of posterior ulcer; C, transverse closure with layer of silk; D, gastroduodenostomy, palpation of low-lying ulcer with distal constriction; E, replacement of guy suture, indication of extension to 8-10 cm.; F, demonstration of low-lying ulcer; G, transverse closure with layer of silk.

portant when the diagnosis is doubtful (see figure). The examining finger can be placed into the more distal duodenum and so enables one to determine the presence of any distal constriction in the duodenum which would make gastrojejunostomy preferable to pyloroplasty. In the case of the bleeding duodenal ulcer, pyloroplasty also allows for direct visualization and immediate control of the hemorrhage by suture ligation of the ulcer.

A Heineke-Mikulicz pyloroplasty with closure affected by single row of interrupted silk,[3] which I have used since 1951, has further added to the efficiency of the pyloroplasty as a drainage procedure and avoids obstruction from subsequent cicatrization. This closure has proved perfectly safe without instance of trouble from leakage. I have continued to use gastrojejunostomy as the drainage procedure in those instances where acute inflammatory reaction or marked scarring or distal constriction are obvious contraindications to pyloroplasty.

Additional help in avoiding the postvagotomy complications of delayed gastric emptying has been achieved by careful attention to the postoperative care in prevention of gastric dilatation, by the use of the nasogastric or gastrostomy tube for four or five days, by prevention of hypokalemia, and, after the beginning of ingestion of food, by adhering to the principle of small amounts taken more frequently and the skipping of a meal in case of feeling of fulness.

Causes for Recurrence

The late complication of vagotomy is recurrence of ulcer or ulcer symptoms and this has been invariably accompanied by return of increase in volume of secretion and increase of acidity due to incomplete vagotomy. In such instances there is significant volume of gastric secretion in the 12-hour overnight collection and significant acid response in insulin-induced hypoglycemia in the test described by Hollander.[4] There is a close correlation between the Hollander insulin test results and my clinical results.

Intractability as a reason for vagotomy has presented most of the problems, both in decision as to whether or not to operate and in the presentation of unsatisfactory postoperative result. This group undoubtedly contains many patients suffering from emotional manifestations which are mistaken for ulcer symptoms. Occasionally, of course, severe emotionally induced symptoms may be accompanied by definite indication for surgical intervention, such as bleeding or perforation, and, although in these patients the ulcer symptoms may subside with the healing of the ulcer, the patient still presents emotional instability and continues to have the symptoms as a result of abnormal physiological activity of the gastrointestinal tract.

In general it is evident in our experience that the best results are obtained in the patient with the worse ulcer, with high acidity and volume of gastric secretion, and with roentgenologic evidence. The poorest results are obtained in the patients with the maximum number of complaints but the fewest abnormal objective signs.

Results

Three hundred twenty-two vagotomy operations were performed for peptic ulcer during the period of 1946-1958. (These include operations in association with Dr. J. R. Higgins.) In the series, 27 patients were treated by vagotomy alone. Ten of these patients were subsequently operated on because of undesirable side-reactions caused by gastric retention. Two patients were thought to have recurrence of the ulcer but were not subjected to reoperation.

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In 29 patients with peptic ulcer treated by subtotal gastric resections, vagotomy was an accompanying procedure in 10.

There were 93 patients with duodenal ulcer who were treated by vagotomy plus gastrojejunostomy. There was one death due to pneumonitis in this group. Of the remaining 92 patients, 64 (70%) secured a good result, 16 (17%) a fair result, and 12 (13%) a poor result.

Of these 93, vagotomy with gastrojejunostomy was performed in 22 (24%) patients with a history of repeated hemorrhages of moderate to severe degree; of these 14 (64%) obtained good results, 4 (18%) a fair result, and 4 (18%) a poor result. In 22 (24%) patients there was a history of perforation; of these 17 (77%) reported good result, 4 (18%) a fair result, and 1 (5%) a poor result. There were 49 (52%) patients operated on for duodenal ulcer with intractable pain and symptoms; 33 (68%) received good results, 8 (16%) fair results, and 8 (16%) poor results.

Forty-three of the above-mentioned patients subjected to vagotomy and gastrojejunostomy were checked by questionnaire; 33 (77%) received an excellent result, 7 (16%) a fair result, and 3 (7%) reported a poor result. Of these 43 contacted by questionnaire, 8 (19%) were operated on because of bleeding; 6 (75%) reported excellent results, 1 (12.5%) a fair result, and 1 (12.5%) a poor result. Ten patients (23%) gave a history of perforation, and of these 9 (90%) reported excellent results and 1 (10%) a fair result. Of 25 (58%) with intractable cases, 18 (72%) secured excellent results, 5 (20%) a fair result, and 2 (8%) a poor result. (In the tabulation the words good and excellent are interchangeable.)

Vagotomy with pyloroplasty was performed in 162 patients with various types of duodenal ulcer. Of these 131 (81%) secured a good result, 25 (15%) a fair result, and 6 (4%) a poor result. Of these 162 cases, 50 (31%) gave a history of repeated hemorrhages of moderate to severe degree; of these 39 (78%) received a good result, 7 (14%) a fair result, and 4 (8%) a poor result. Thirty-two (20%) gave a history of perforation; of these 26 (81%) achieved a good result and 6 (19%) a fair result. Eighty (59%) were operated on because of intractable pain; of these 66 (82%) secured a good result, 12 (15%) a fair result, and 2 (3%) a poor result.

The results have been analyzed from the last 121 patients with duodenal ulcer who were operated on by vagotomy and pyloroplasty. There were no deaths in this group; 87 (71%) obtained an excellent result, 30 (25%) fair results, and 4 (4%) poor results.

Of these 121 patients 36 (30%) gave a history of bleeding and of these 28 (77.7%) obtained excellent results, 7 (19.4%) fair results, and 1 (2.7%) poor results. Twenty-eight patients (23.3%) gave a history of perforation; of these 21 (75%) obtained excellent results, 6 (21.4%) fair results, and 1 (3.5%) poor results. Fifty-seven (47.5%) of these 121 patients were operated on because of intractability; 38 (66.6%) obtained excellent results, 17 (30%) fair results, and 2 (3.4%) poor results.

There were two deaths in the entire series of operations for an operative mortality of 0.6%. One of these deaths was for pneumonitis as mentioned above, and one death was in a patient who had had recurrent attacks of bleeding five years after a vagotomy with gastrojejunostomy, and a transthoracic supradiaphragmatic vagotomy was then performed. The patient died on the seventh postoperative day from myocardial infarction. No deaths have occurred after the vagotomy pyloroplasty operations.

Of 92 patients who had vagotomy and gastrojejunostomy, there were 12 reported poor results excluding the one death. Seven were operated on again; five because of the development of marginal ulcer, one because of the occurrence of gastric ulcer, and one because of improperly placed gastrojejunostomy with inordinately long afferent jejunal limb. Three other patients had proved marginal ulcer but did not consent to further surgery.

Of those 162 patients treated by vagotomy and pyloroplasty 6 (4%) were reported as poor results. Three of these were operated on again, two had subsequent gastrojejunostomy because of poor emptying, and one had a gastric resection because of recurrence of the ulcer.

Thirty-one patients were women, constituting 10% of the total operated on. Five of these were considered to have unsatisfactory results, with two recurrences. Two of these patients were operated on again, both because of gastric retention. One operation consisted of a revision of the gastrojejunostomy which had been done in conjunction with the original operation of vagotomy. The first gastrojejunostomy had proved unsatisfactory as a drainage procedure because of an inordinately long afferent jejunal limb. The other patient originally had a vagotomy and an accompanying pyloroplasty. Because of the considerable scarring in the region of the ulcer, the pyloroplasty proved unsatisfactory as a drainage procedure and a gastrojejunostomy subsequently had to be performed. This should have been done at the time of the vagotomy, considering the amount of inflammatory edema and scarring that was present when the pyloroplasty and vagotomy were done.

Results were classified as excellent when the patient was completely relieved of symptoms and had no undesirable side-reactions related to the vagotomy operation; fair when the patient was free of ulcer symptoms and was improved over the preop-

erative condition but still had one or more minor symptoms of gastrointestinal nature; and poor when the patient was worse than before operation and had a proved recurrence.

The significant postoperative undesirable side-reactions listed by the patients in order of decreasing frequency were fulness or bloating, loss of appetite, diarrhea, and loss of weight. The questionnaire asked for the length of time that the patient had symptoms before surgery was performed; overall results of surgery, namely, excellent, fair, or poor; and complications after surgery, namely (although eating well and with good appetite), excessive gas on stomach, vomiting, diarrhea, pain after eating, bleeding, return of ulcer, necessity of secondary operation, loss of weight, or gain of weight.

Cardiospasm, although not specifically brought out in the questionnaire, was known to have occurred to a troublesome degree in only a few patients and was demonstrable roentgenographically in only one patient. In all others the symptoms were transient.

This review indicates that vagotomy with pyloroplasty or gastrojejunostomy is a highly satisfactory surgical procedure for dealing with duodenal ulcer. The mortality is lower than that known with other surgical procedures for duodenal ulcer. Failures are due to recurrence of ulcer, antral stasis, and inadequate postoperative care. The most objectionable features are the undesirable side-effects of fulness and intermittent diarrhea and these have been proved transient in nature and can be controlled by a distally placed small gastrojejunostomy or by pyloroplasty and by adequate postoperative care including avoidance of gastric dilation with nasogastric or gastrostomy tube during the immediate postoperative period.

Conclusions

Pyloroplasty now best eliminates antral stasis and regurgitation of jejunal contents into the stomach mucosa, affords excellent visualization of the ulcer area, and facilitates subsequent operative procedures in case of incomplete vagotomy with recurrent ulceration or perforation. Recurrence is invariably accompanied by a return of acidity and increased volume of secretion and is due to incomplete vagotomy. Pyloroplasty as advocated has proved a simple safe drainage procedure.

Vagotomy is not an answer to a psychological problem but it can reasonably be stated that vagotomy with pyloroplasty will give the patient a better than 99.4% chance of surviving the operation and a 96% chance that he will be relieved or improved. In view of these facts, which seem evident, I believe vagotomy is rational, safe, and efficient and the most conservative procedure at the present for solving the problem of the ulcer diathesis.

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FACTORS IN THE REDUCTION OF INFANT MORTALITY.—Every State, without exception, succeeded in reducing its infant mortality rate in the decade between 1945-46 and 1955-56. . . . In 31 States and the District of Columbia the decrease amounted to 25 percent or more. In New Mexico the infant mortality rate fell no less than 56 percent—from 89.5 to 39.5 per 1,000 live births. Maine and West Virginia each recorded a reduction of somewhat over 40 percent. Whereas one third of the States had infant mortality rates of at least 40 per 1,000 in 1945-46, not a single State was in that category a decade later. . . .

All the major causes of infant mortality, except postnatal asphyxia, showed a decline in the decade under review. The death rate from the gastro-intestinal diseases—gastritis, dysentery, and diarrhea of the newborn—fell from 2.4 per 1,000 live births in 1945-46 to 0.9 in 1955-56, a drop of more than 60 percent. For whooping cough, the reduction in mortality amounted to about 75 percent; the other three communicable diseases of childhood—measles, scarlet fever, and diphtheria—have been reduced to vanishing proportions as causes of death in infancy. Among the major factors accounting for the improved control over the infections in infancy have been the widespread use of antibiotics, immunization procedures, improved nutrition, increased pre- and postnatal medical care, and a rise in the general standard of living.—Recent Trends in Infant Mortality, *Statistical Bulletin*, May, 1959.

CHANGES IN BLOOD VOLUME DURING USE OF ARTIFICIAL KIDNEY

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These preliminary studies indicate that empirical methods of controlling fluid balance of a patient during extracorporeal dialysis are fraught with many hazardous unknowns. Changes in plasma volume, red blood cell volume, and total blood volume during dialysis were determined by one group of workers, while another group performed the dialysis and regulated hydration empirically, as is customary. Actual measurements were later compared with the clinical estimates of the patient's needs. Marked disparities were found to exist. A firm basis for satisfactory regulation of hydration during dialysis would be afforded by the routine incorporation of blood volume studies during extracorporeal dialysis.

Extracorporeal dialysis with the artificial kidney has gained an accepted place in the treatment of a variety of conditions. Specific indications have been discussed in detail by Kolff and others.[1] The results to be sought are the removal of undesirable metabolites from the body and the restoration of a normal electrolyte balance. Secondary effects, which have not as yet been completely documented, are the concomitant alterations of plasma volume, red blood cell volume, and total blood volume which occur as an indirect response to the treatment.

That such secondary changes in blood volume occur during the procedure is widely recognized, and careful attention is given to their prevention and control on an empirical basis.[2] However, our work indicates that in these patients unsuspected discrepancies often exist between clinical appearance and actual state of hydration. As a search of the literature has failed to disclose other reports of the actual measurements of blood volume, plasma volume, and red blood cell volume during dialysis, it is our hope that publication of our findings may focus further attention on this phase of dialysis with ultimate benefit to the patient.

In essence, the dialyzing procedure involves the shunting of the patient's blood outside his body and along one side of a semipermeable membrane which is bathed on the other side by a carefully prepared dialyzing solution. Waste metabolites pass through this membrane into the dialyzing solution and are carried away, while plasma electrolytes assume equilibrium with those in the dialyzing solution.[3]

Alterations in body fluids occur concomitantly as fluids pass back and forth through this membrane. These fluid changes are contingent on the hydrostatic pressures within the dialyzing chambers, the respective osmolarities of the dialyzing solution and of the blood, and the state of hydration of the patient. As many of these patients already have severe fluid imbalance and, often, severe anemia as well, relatively small shifts in fluid balance can have serious consequences. Fortunately, such alterations can be readily adjusted once observed.

Customarily, regulation of these fluid components is carried out on an empirical basis. For example, dialysis generally tends to dehydrate the patient. This is readily corrected by administration of intravenously given fluids during the procedure. Conversely, overhydration or pulmonary edema may exist. In this case the excess fluid may be removed by the addition of hypertonic dextrose solution to the dialyzing bath and by increasing the filtration pressure within the dialyzing unit.[4] In other instances the blood picture may be severely altered by preexisting blood loss or anemia. This is readily corrected by administration of blood and fluids during the dialysis. However, our studies have shown that a clinical estimate of the patient's fluid status may be misleading, and regulation of fluid balance solely on this basis may be surprisingly inaccurate.

Method

To study these fluid changes, serial blood volume determinations were performed on the patients undergoing extracorporeal dialysis. Determinations of the total blood volume, plasma volume, and red blood cell volume were done in each case by our technologists immediately before dialysis and promptly afterward, and, in some instances, during the procedure. Meanwhile, regulation of fluids proceeded as is customary, on an empirical basis. After the dialysis, the results of the blood volume studies were compared with the clinical impressions which had been noted for corresponding periods. Such comparisons indicated that marked discrepancies were present between the clinical impressions and

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the actual measurements. It was generally felt that this was due to an inherent delay between internal physiological changes and their external manifestations.

The Kolff disposable twin coil dialyzing unit was used throughout these procedures. It is efficient, readily set up, and precludes the need for time-consuming sterilization.[3] The blood volume determinations were done by the gravimetric isotope procedure, reported by Zipf and co-workers,[4] which has been in routine clinical use for over four years. Results of this test are available 20 to 30 minutes after request and, when used in conjunction with dialysis, permit adjustments of fluids to follow the physiological course of the treatment.

Results

The results of this series are shown in the accompanying table. Both predialysis and postdialysis status of the various vascular components in each patient are indicated as compared to the ideal volumes calculated on the basis of height and weight. Also shown is whether dialysis increased or decreased the patient's plasma volume, red blood cell volume, and total blood volume. It should be borne in mind that these figures were not made available to the dialyzing team until after termination of the dialysis.

Total Blood Volumes, Red Blood Cell Volumes, and Plasma Volumes Before and After Dialysis

		Vol., Ml.								
		Actual Compared to Ideal*						Calculated Alteration During Procedure		
		Before Dialysis			After Dialysis					
Case No.	Dialysis, Times	Plasma	Red Blood Cell	Total Blood	Plasma	Red Blood Cell	Total Blood	Plasma	Red Blood Cell	Total Blood
1	Only	−107	−1,341	−1,448	−761	−1,320	−2,084	−657	+21	−636
2	1st	+513	−878	−365	+547	−793	−226	+34	+95	+129
	2nd	−890	−897	−1,788	+143	−657	−514	+1,039	+240	+1,279
3	1st	+186	−222	−36	−225	−183	−408	−411	+39	−372
	2nd	+104	−374	−270	−237	−224	−461	−344	+150	−194
4	Only	+1,411	−292	+1,119	+913	+140	+1,053	−498	+432	−66
5	Only	−468	−298	−766	−302	−783	−1,085	+166	−405	−319
6	2nd	+74	−866	−792	−427	−528	−955	−491	+338	−153

* Ideal volumes calculated on basis of height and weight

Report of Cases

Case 1.—A 60-year-old man was admitted to the Miami Valley Hospital, Dayton, Ohio, with mild uremia and acute urinary retention due to prostatic obstruction accompanied by an exacerbating chronic pyelonephritis. The blood pressure was 200/104 mm. Hg; pulse was 100 beats per minute and of poor quality. An electrocardiogram showed an old posterior wall infarction. The erythrocyte count was 2,900,000 per cubic millimeter. The hemoglobin level was 8.6 Gm.%, and the leukocyte count was 13,950 per cubic millimeter, with granulocytes predominating. Urine cultures showed Aerobacter aerogenes. The patient was treated medically for six weeks without response, and the blood urea nitrogen level continued to rise. The patient became disoriented when this level reached 120 mg. per 100 ml., at which time a dialysis was performed. In six hours the blood urea nitrogen level dropped to 35 mg. per 100 ml. and the creatinine level dropped from 7.2 mg. per 100 ml. to 4.1 mg. per 100 ml. Subsequently his general condition was much improved. The inflammatory process in the genitourinary tract subsided with antibiotic therapy. He was discharged 11 days after dialysis and was seen afterward as an outpatient. Six months later he was still improved, ambulant, and alert, maintaining a blood urea nitrogen level of 50 mg. per 100 ml. and a hemoglobin level of 10 Gm.%.

Case 2.—A 44-year-old man, an alcoholic, had had a partial gastrectomy for gastric ulcers 12 years prior to this admission. He was admitted to the hospital in shock after severe hematemesis. A diagnosis of recurrent ulcers with hemorrhage was made. He was given supportive therapy and operated on, at which time an additional portion of stomach was removed. Transfusion of 21 units of blood was necessary during this episode.

He subsequently showed anuria and became incoherent. Three days after operation the blood urea nitrogen level was 115 mg. per 100 ml., the potassium level was dangerously high, and it was necessary to relieve the uremia by dialysis. After dialysis his over-all condition improved and he was again rational.

Melena and hematemesis persisted during the next week. A severe peritonitis developed. During this period he received three additional dialyses, each time responding well clinically and physiologically and each time returning rapidly to predialysis status. Prior to each dialysis there were cardiac irregularities and chest pains, assumed to be due to hyperkalemia; the potassium level at one time reached 36.7 mg. per 100 ml. These symptoms would disappear after an hour of dialysis. Several hours after the fourth dialysis the patient went into irreversible shock and died within 10 hours. Au-

topsy disclosed 4,000 ml. of purulent exudate in the peritoneum, with necrosis around the anastomosis and active hemorrhage into the intestine.

Case 3.—An 8-year-old boy was admitted with uremia and a blood pressure of 220/140 mm. Hg; he had been given a diagnosis of chronic glomerulonephritis. The blood urea nitrogen level was 188 mg. per 100 ml., creatinine level 6.2 mg. per 100 ml., carbon dioxide–combining power 33 vol.% per 100 ml.; and hemoglobin level 10.7 Gm.%. Although the prognosis was poor, dialysis was attempted.

After the first dialysis the blood urea nitrogen level was 64 mg. per 100 ml. and the creatinine level was 3.1 mg. per 100 ml. Blood pressure dropped to between 130/100 and 170/120 mm. Hg and remained in that range for several days. Five days after dialysis the blood urea nitrogen level had risen to 212 mg. per 100 ml. and a second dialysis was done.

Improvement was again temporary, and no further dialyses were attempted in view of the obvious chronicity and irreversibility of the process. He was taken home and several days later died. Autopsy permission was not obtained.

Case 4.—A 70-year-old woman with a history of pyelonephritis was admitted to the hospital with congestive heart failure, uremia, and thrombophlebitis of the legs associated with cellulitis. Blood cultures showed the presence of hemolytic staphylococci. The blood urea nitrogen level was 154 mg. per 100 ml., creatinine level 9.1 mg. per 100 ml., potassium level 24.6 mg. per 100 ml., and carbon dioxide–combining power 25 vol.% per 100 ml. The patient was incoherent and in a critical condition. Dialysis was suggested to relieve the azotemia and allow time for a response to antibiotics and supportive therapy.

After four hours of poorly tolerated dialysis, the procedure was terminated. The blood urea nitrogen level had dropped to near normal and the carbon dioxide–combining power increased to 40 vol.% per 100 ml. Her condition appeared satisfactory during the night, but respiratory distress developed in the morning and she died shortly thereafter.

Autopsy showed severe prolapse of the pelvic organs with ureteral obstruction, bilateral hydroureters, and a severe ascending pyelonephritis. Bacteremia was still present. The lungs showed severe pulmonary congestion and edema, with atelectasis and diffuse inflammation.

Case 5.—A 34-year-old woman with an established diagnosis of polycystic kidneys was treated medically to combat electrolyte imbalance and uremia. She ultimately developed electrocardiographic indications of hyperkalemia. Although the irreversible nature of her condition was recognized, it was hoped dialysis might offer a remission of several months.

At the beginning of the procedure she was irrational and restless; the blood urea nitrogen level was 190 mg. per 100 ml. and the potassium level 30.5 mg. per 100 ml. During the dialysis her mind cleared and eventually she began to converse rationally. The electrocardiogram changes characteristic of potassium intoxication disappeared. After six hours of dialysis, the blood urea nitrogen level was 39 mg. per 100 ml. and the blood potassium level 18.7 mg. per 100 ml.

Several days later the blood urea nitrogen and potassium levels began to rise rather rapidly. Further dialyses were not attempted. She died in uremia 36 days after dialysis. Autopsy revealed immense polycystic kidneys bilaterally with little functional renal tissue remaining.

Case 6.—A 14-year-old girl who had not previously seen a physician was hospitalized with nausea, vomiting, and a severe anemia. Several units of blood were given without incident. Two days later she developed complete anuria, and uremia developed rapidly.

She was transferred to this hospital with her condition as yet undiagnosed. She was comatose and having repeated generalized convulsions. There was severe pulmonary congestion and edema with frothy fluid exuding from the mouth. Heart rate was 116 beats per minute with a suggestion of a gallop rhythm. An electrocardiogram showed right bundle-branch block and absence of P waves. Blood pressure was 164/112 mm. Hg. blood urea nitrogen level 174 mg. per 100 ml., potassium level 25 mg. per 100 ml., carbon dioxide–combining power 28 vol.% per 100 ml., sodium level 280 mg. per 100 ml., and chloride level 500 mg. per 100 ml. Death was imminent, and immediate dialysis was instituted.

After six hours of dialysis she was much improved and could answer questions coherently. The electrocardiogram the next day was essentially normal, and the patient was feeling well enough to read. Four days later a second dialysis brought the blood urea nitrogen level down to 34 mg. per 100 ml. Urinary output slowly increased and a week later reached 500 ml. daily. The ability of the kidneys to concentrate urine never returned, however, and specific gravity remained below 1.010.

In her improved state, retrograde pyelography was done and revealed severe hypoplasia of the right kidney and marked dilatation and blunting of the calyceal system on the left, indicating a chronic inflammatory process. She died in uremia five weeks after the initial onset of anuria.

Autopsy showed both kidneys to be hypoplastic, the right being less than 1 in. long. Characteristic findings of chronic glomerulonephritis were also present, with little functional tissue remaining. The uterus and ovaries were correspondingly small and hypoplastic.

Comment

In the average healthy person a delicate balance exists between the total blood volume, plasma volume, red blood cell mass, and interstitial and intracellular fluids. In the patient in renal failure, with retention of fluids and concomitant electrolyte disturbances, this balance is markedly altered. The addition of extracorporeal dialysis in such a situation compounds the existing variables of fluid balance control and adds to the difficulties of proper clinical evaluation. Consequently, during dialysis the physician must be constantly alert to manifestations of altered hydration. When clinical signs appear he must act promptly to restore the fluid levels to more optimal states. He can do this by altering hydrostatic pressure within the dialyzing unit, by changing the dextrose concentration of the dialyzing solution, thus altering osmotic pressures, or by administering selected amounts of blood, plasma, or fluids to the patient.

However, accurate evaluation of these needs is difficult and misleading, as changes are often not promptly manifest externally or witnessed immediately. In each of our cases, constant attention was paid to the state of hydration of the patient and all efforts were made during dialysis to maintain optimum hydration and blood volume. Clinical observations indicating blood or fluid loss or overhydration were honored immediately by prompt efforts at adjustment. Subsequent comparison of these observations with the corresponding blood volume determination results showed that clinical impressions had generally afforded insufficient grounds upon which to base fluid regulation and offered poor means of judging the end-point. In each case, later developments indicated that the measurements made by the isotope method had foreshadowed the subsequent clinical course, thus reflecting the accuracy and the value of such measurements in this type of work. In most cases, fluid levels could have been held much closer to desired levels had they been based on these measurements rather than on clinical judgment. It is our feeling that such determinations should be adopted routinely in work with the artificial kidney.

These preliminary studies indicate that empirical methods of controlling the fluid balance of a patient during extracorporeal dialysis are fraught with many hazardous unknowns. The incorporation of the serial blood volume studies, before, during, and after the procedure provides a precise indication of steps required to adjust the fluid needs of the patient. The radio-iodinated (I^{131}) serum albumin (human) (Risa) gravimetric method of determining these as described in this report is simple, precise, rapid, and well suited to such a use. It offers the physician in charge of dialysis an excellent supplement to clinical judgment, gives him a sound basis for his decisions, and can aid greatly in helping him achieve his goal of a more efficient and beneficial dialysis.

Summary

Determinations of changes in the plasma volume, red blood cell volume, and total blood volume during a series of dialyses with the artificial kidney were carried out by one group of workers, while another group performed the dialyses and regulated hydration empirically, as is customary. Actual measurements were later compared with the clinical estimates of the patients' needs. Marked disparities were found to exist between the clinically manifest conditions and the actual levels of hydration as measured. Therefore, a firm basis for regulation of hydration during dialysis would be afforded by the routine incorporation of blood volume studies during extracorporeal dialysis.

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RADIOLOGIC CONTRIBUTIONS TO THE DIAGNOSIS OF HISTOPLASMOSIS

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A study was made of 74 pediatric patients selected because they had given negative tests with tuberculin but positive tests with histoplasmin. The purpose was to identify symptoms and findings useful in the diagnosis of histoplasmosis. In half of the children symptoms of acute respiratory infection were present. There were 12 children in whom the only symptoms of illness were gastrointestinal, consisting of nausea, vomiting, and, occasionally, abdominal pain. Chest roentgenograms showed hilar calcifications in 32 (50%) and perihilar lung infiltrates in 10 (15%) of 67 cases, but the patterns varied. Diagnosis is difficult because it may no longer be possible to isolate Histoplasma capsulatum from specimens taken five months after the infection and because five years or more may elapse before the chest roentgenograms become positive for calcification. In patients with positive reactions to histoplasmin and negative reactions to tuberculin, the presence of an isolated lung infiltrate or miliary involvement with hilar adenopathy should suggest a diagnosis of histoplasmosis.

A recent report showed that in 1958 over 30 million people had been infected with Histoplasma capsulatum in the central United States,[1] and an increasing number of reports are being written about patients with histoplasmosis. The once "rare lung disease" is now occurring frequently in the endemic areas. The end-results of old histoplasmosis are being seen over wider areas of the country as the population expands and shifts. In some nonendemic regions sensitivity to histoplasmin has been found to be even higher than that to tuberculin.[2] A greater emphasis should be placed on helping to suggest the diagnosis at the stage when this becomes significant: although the diagnosis of histoplasmosis cannot rest solely on the roentgenographic examination, the radiologist is sometimes able to suspect it and include it in his differential diagnosis.

There are many reports dealing with the calcifications caused by histoplasmosis which are found long after the acute period of the disease is over. Although it is important to differentiate the origin of such calcium deposits as produced by histoplasmosis, tuberculosis, or other disease, it is better to attempt to recognize the early manifestations of histoplasmosis, as many cases go undetected, diagnosed as mild subclinical respiratory infections.

Extensive epidemiologic studies have been done, and results are found grouped together with clinical, pathological, and laboratory reports in an extensive monograph.[3]

Clinical Features

Histoplasmosis is a relatively benign pulmonary disease, which sometimes occurs in epidemics. It is more prevalent in infants and children, but it may occur at any age, adults being infected more often with the epidemic type. Respiratory manifestations are most common, and gastrointestinal symptoms are next in occurrence. Febrile episodes are present and commonly associated with upper respiratory infections. In this study I found that 19 of 74 patients had cervical adenopathy. The presence of enlarged liver and spleen occurs at times and has been regarded as highly suggestive of histoplasmosis in infants and children from endemic areas.[4] The severity of the disease varies from the mild infection lasting one to four days to the severe forms that can sometimes be fatal.[5]

The disease can be discovered by the histoplasmin skin test, which gives positive results with higher titers within two to four weeks after the onset of the disease. The serologic proof of infection is given by the complement-fixation test, and the definite diagnosis can be made after obtaining the fungus, although this cannot always be accomplished because H. capsulatum may no longer be detected in the lung and lymph node lesions five months after the infection.

Histoplasma can be found contaminating the habitat of pigeons and domestic fowl, and patients living close to or in contact with these birds are sometimes found to have a history of a rather mild respiratory infection. These patients give a positive response to the histoplasmin skin test, and the radiologist is most likely to find evidence of calcifications in the lungs and sometimes elsewhere.

Pathological and Roentgenographic Features

There is no typical roentgenographic or histopathological pattern for lesions found in histoplasmosis. Pulmonary involvement is found in half of the patients,[6] but any other organ can be involved. The so-called early exudative phase of the pulmonary lesion is not as well known as the old healed calcified lesions seen in one-half of the patients and sometimes mistaken for a Gohn focus of tuberculosis. Although it has been said that the antemortem diagnosis of histoplasmosis is not possible,[5] the

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information from the radiologist together with the results of the skin test and serologic study helps the clinician to make a diagnosis.

The primary lesion in the lung can be a single, discrete, and clearly defined nodular infiltrate, located in the peripheral lung zones, alone or associated with secondary involvement of the hilar nodes (fig. *A*). Large lesions represented by irregular patches of consolidation scattered throughout both lungs have been reported.[7] The development of these infiltrates has been carefully observed and correlated with serologic proof of histoplasmosis.[8]

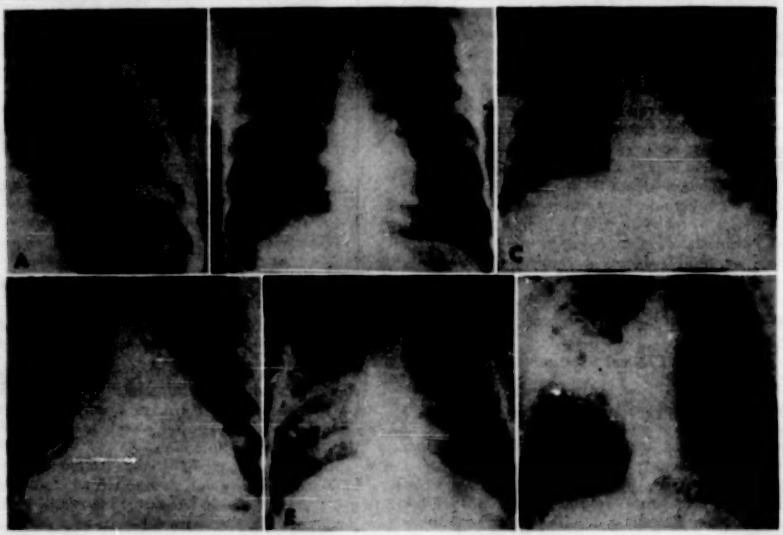
Another manifestation of pulmonary histoplasmosis is the miliary involvement with small nodular lesions or a diffuse granular miliary pattern scattered throughout both lung fields (fig. *B*). This picture has been regarded by some as consistent with the terminal stage of the disease[5] but is present in many patients who live. In other instances, there is only involvement of the hilar nodes with short radiating perihilar infiltrates (fig. *C*) which may become confluent and form a patch of incomplete consolidation (fig. *D*). Typical lobar distribution sometimes occurs (fig. *E*); pleurisy is rare.

A more extensive involvement is found in the so-called chronic progressive histoplasmosis[4] in which a large fibrotic mass, sometimes with cavitation, can be seen. This type cannot be differentiated from a tuberculous lesion of the lung (fig. *F*).

In some patients, especially infants, extrathoracic involvement occurs and the only clue found by the radiologist may be the presence of an enlarged liver and spleen at the time of the x-ray examination of the chest, if the upper abdominal regions are included.

Submucosal ulcerations in the gastrointestinal tract and caseation of the adrenal glands have been reported but cannot be visualized in the roentgenograms.

The lesions tend to calcify several months after the initial infection subsides, and two to five years later these calcium deposits can be seen in the roentgenograms. They are commonly found in the lung and can be single or miliary, peripheral or confined to the hilar regions and nodes. There may be only an isolated focus in the periphery of the lung with a central core of calcification and a halo. "Mulberry" and "stippled" calcifications have been described as suggestive or typical of the disease.[9] Extrapulmonary calcifications have been seen in the splenic area of some patients, the fungus being demonstrated within the calcified lesion.[10] Lesions in the brain and bone are rarely seen, although the presence of osteitis has been reported in a child with generalized histoplasmosis.[11]



X-rays of six patients with histoplasmosis. *A*, isolated infiltrate in lung of patient with positive reaction to skin and complement-fixation tests for histoplasmosis. *B*, extensive miliary involvement of lungs; histoplasmin skin test reaction positive, tuberculin negative. *C*, bilateral hilar adenopathy and fine, radiating perihilar infiltrates; positive reaction to serologic and skin tests. *D*, area of incomplete consolidation at right infrahilar region. *E*, lobar consolidation; histoplasmin skin test reaction positive, tuberculin negative. *F*, extensive involvement of right upper lobe with cavitation; Histoplasma capsulatum obtained from mass after surgical removal.

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Review of Cases

Of 305 admissions to the pediatrics department of the Johnson Memorial Clinic at Abingdon, Va., in one year, 40 patients were selected who gave a positive reaction to histoplasmin. Another 40 children from the outpatient group in the same period also showed positive results on the skin test. In 62 of these patients, enough information was available to warrant study of their cases. All gave negative reactions to a tuberculin test. Serologic proof of histoplasmosis was obtained in 12 patients who gave positive reactions to the complement-fixation test with histoplasmin or yeast-phase cells.

In half of these children, symptoms of acute respiratory infection were present with cough and fever, accompanied in some cases by gastrointestinal symptoms. The latter appeared in 12 patients as the only manifestation of the disease and consisted of nausea, vomiting, and, occasionally, abdominal pain. In 16 patients, cervical nodes were detected. Three showed an enlarged liver and spleen and two had enlargement of the liver alone (table 1).

A second group of 12 patients was obtained in a two-year period from the Research and Educational Hospitals, University of Illinois. These patients had positive reactions to histoplasmin and negative reactions to tuberculin skin tests. Respiratory symptoms were common; three patients had palpable cervical nodes and two showed an enlarged liver and spleen.

Of the 74 patients from the two groups, 67 had x-ray studies available. In 22, definite signs of parenchymal lung disease were found in various patterns. Associated hilar adenopathy occurred in 7 and appeared as a single manifestation in 19. Intrathoracic calcifications of varied appearance were seen in 43 patients and occurred more commonly at the hilar and perihilar regions. The miliary type of calcium deposits in the lungs were found in three patients. No splenic calcifications were seen (table 2). The possibility of histoplasmosis was mentioned in 12 roentgenographic reports.

TABLE 1.—*Clinical Findings in Seventy-four Patients with Histoplasmosis*

	Group A (62)	Group B (12)	Total (74)	
			No.	%
Respiratory symptoms	27	6	33	45
Gastrointestinal symptoms	12	3	15	20
Fever	25	4	29	40
Splenomegaly	3	2	5	7
Hepatomegaly	5	3	8	10
Cervical nodes	16	3	19	25

Comment

The increasing incidence of histoplasmosis is evident. The more widespread use of the histoplasmin skin test may account for the discovery of more cases. This test constitutes a fairly good screening procedure in the endemic regions. Data available at present indicate that the diagnosis of histoplasmosis can be reliably made by proper serologic methods.[3] The confirmation by isolation of the fungus cannot always be obtained except at operation on postmortem examination.

A patient coming from an endemic area with respiratory and/or gastrointestinal symptoms, with a febrile episode of unknown origin, and a history of contact with pigeons or fowl should at least be suspected of having histoplasmosis. The task of the radiologist is to suspect and mention this possibility. The presence of an isolated lung infiltrate or miliary involvement of the lungs with hilar adenopathy should be suggestive of histoplasmosis in these patients with positive reactions to histoplasmin and negative reactions to tuberculin tests.

TABLE 2.—*X-Ray Findings in Sixty-seven Patients with Histoplasmosis*

	No.	%
Lung infiltrates		
Single	2	3
Miliary	2	3
Perihilar	10	15
Bronchopneumonic	4	6
Lung calcifications		
Miliary	3	4
Hilar	32	50
Peripheral	8	12
Pneumonic consolidation	4	6
Hilar adenopathy	26	40
Splenic calcifications	0	0

In the case of miliary involvement of the lungs, the important differential is with other fungus infections, diffuse bronchopneumonia, tuberculosis, sarcoidosis, and pneumoconiosis. This type is not always fatal, as proved by the presence of miliary calcifications, frequently representing healed miliary histoplasmosis, in the lungs of some patients.

When tuberculosis and other fungus infections can be excluded, the presence of a large granulomatous lesion in the lung could be an indication of histoplasmosis, although this may not be confirmed unless operation is performed.

Calcifications and their differential diagnosis are not so important; five years or more may be required for the lesions to show up in the roentgenogram. The assistance to the clinician then is minimal compared to that offered in early stages of the disease.

The development of the so-called middle lobe syndrome in patients, whose infected hilar nodes heal by fibrosis and calcification constricting a bronchus is mentioned by Furcolow and associates.[4a] These patients may have negative reactions to cultures and microscopic examinations for fungus, although the disease is caused by histoplasmosis.

Patients who have an acute episode of histoplasmosis with fresh lung infiltrates visualized at the same time as lung calcification may possibly have recurrence of the disease, although this has been regarded as uncommon. The occurrence of bronchioliths has also been referred to as one of the complications occasionally found.

Summary

Although histoplasmosis is difficult to diagnose, information from the radiologist and results of histoplasmin and tuberculin skin tests and serologic

study can help the clinician. The role of the radiologist is important in the recognition of this disease in the early stage, especially since five years or more may be required for calcified lesions to show in the roentgenogram. Confirmation of diagnosis can not always be obtained by isolation of the fungus, as Histoplasma capsulatum may no longer be detected in the lung and lymph node regions five months after the infection.

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BLEEDING DUODENAL ULCER

STUDY OF ONE HUNDRED SIXTY-TWO PATIENTS, WITH PARTICULAR REFERENCE TO PAIN, SEASONAL INCIDENCE, AND BLOOD GROUPS

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Data relating the course of abdominal pain to the severity of bleeding from duodenal ulcers were obtained from 162 patients, in each of whom the diagnosis had been established by contrast roentgenography, operation, or autopsy. Among 45 patients with minimal bleeding, 4 experienced some relief of pain, while among 26 patients with moderate to severe bleeding, 7 experienced some relief of pain. Thus, relief from pain occurred more frequently in association with the more severe episodes of bleeding. In this group of patients the more severe hemorrhages were also associated with advancing age, with the fall and winter months of the year, and with a slightly increased frequency of blood group O. These facts suggest that in seeking the cause of gastrointestinal hemorrhage, greater stress should be placed on the pain pattern.

It is a popular belief that the pain of duodenal ulcer disease disappears with the onset of hemorrhage.[1] The present report was prompted by a desire to establish the frequency and validity of this finding, in view of our clinical impression that the contrary was often true.

The records of all the male patients with proved duodenal ulcer disease admitted to the U. S. Naval Hospital, Philadelphia, between Oct. 15, 1953, and Oct. 15, 1958, have been reviewed. The only patients included in this study were those in whom a duodenal ulcer crater was demonstrated by contrast roentgenography, operation, or autopsy. A total of 902 patients fulfilled this criterion, and, of these, 162 (139 Caucasians and 23 Negroes) manifested gross bleeding of varying severity. No patients in whom the bleeding was occult have been included. This report is based on the study of these 162 patients with bleeding duodenal ulcers.

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Severity of Hemorrhage

The severity of the bleeding was graded according to previously described criteria,[3] with the establishment of three groups: minimal hemorrhage, with the hematocrit value remaining above 35% and the patient not given transfusion; moderate hemorrhage, with the hematocrit value remaining above 25% and the patient receiving less than 2,500 ml. of blood; and severe hemorrhage, with the hematocrit value dropping to 25% or less or the patient requiring 2,500 ml. or more of blood or both. The hemorrhage was severe in 27 (16.7%) of the 162 patients, moderate in 58 (35.8%), and minimal in 77 (47.5%).

Hematemesis occurred in 75 (46.2%) of the patients and of these only 9 (12%) had severe bleeding. This would suggest that hematemesis by itself is not necessarily a clear-cut indication of severe hemorrhage, a fact which has been commented on by other authors.[2]

A history of syncope concomitant with the onset of duodenal ulcer bleeding was obtained in 33 (20.3%) of the patients, and, of these, 26 (78.8%) had moderate or severe bleeding. Thus, it can be inferred that syncope commonly heralds a massive hemorrhage.

TABLE 1.—*Relationship of Previous Gastrointestinal Hemorrhage to Severity of Current Bleeding Episode*

Severity	Previous Bleeding		No Previous Bleeding	
	No.	%	No.	%
Minimal	25	46.3	52	48.1
Moderate	21	38.8	37	34.2
Severe	8	14.8	19	17.6

Fifty-four (33.3%) of the patients were noted to have had a previous upper gastrointestinal hemorrhage. As can be seen in table 1, there is no significant difference in the severity of bleeding between those who had and those who had not had previous episodes. This finding is in keeping with current concepts[3] and is contrary to the old belief that repeated bleeding in patients with chronic duodenal ulcer disease is usually attended by a progressive increase in severity with successive occurrences.

The relationship of age to severity is illustrated in table 2. The youngest in the group was 19 years of age, and the oldest was 76. The peak incidence was in the second, third, and fourth decades. Of the total group, 24 (14.8%) were over 60 years of age; this percentage is lower than has been noted by others[2] and may in part be attributed to the predominance of the younger patients seen in this hospital. It is noted that the ratio of the number of severe hemorrhages to the total number of cases for a given decade increases progressively with advancing age. That the older person tends to bleed more severely from duodenal ulcers is generally accepted, although this concept has recently been refuted in a review of 235 patients with bleeding duodenal ulcer by Gardner and Baronofsky.[4]

Pain

The presence or absence of pain, considered to be compatible with that of duodenal ulcer disease, was recorded in 132 of the total 162 patients with bleeding duodenal ulcer. The information was considered inadequate in the remaining 30 patients. In

TABLE 2.—*Relationship of Age to Severity of Bleeding*

Age, Yr.	Total No.	Severity: Minimal, No.	Moderate, No.	Severe No.	Severe %
10-20	3	3	0	0	0
20-30	32	14	15	3	9.3
30-40	57	29	18	10	17.5
40-50	35	15	15	5	14.3
50-60	11	7	2	2	18.2
60-70	14	5	6	3	21.4
70-80	10	4	2	4	40.0
Total	162	77	58	27	

the 132 cases in which pain was documented, 61 patients (46.2%) had no associated pain or distress with or preceding their bleeding episode, 11 (8.3%) had distinct relief of preexisting pain, and 60 (45.4%) had no relief of their pain—indeed, 11 of this latter group noted exaggeration or onset of their pain at the time of the hemorrhage. Burger and Hartfall[5] reported a higher incidence of pain relief in their series, although no comment was made as to the severity of the bleeding in relation to the pain relief. The mechanism by which pain is alleviated during hemorrhage has been variously attributed to the buffering action of the extravasated blood, gastric atony, coating of the ulcer crater with blood, and intense therapeutic management.[6]

In comparing the degree of severity of the hemorrhage to the presence, absence, or alleviation of pain, a distinct correlation was observed (table 3). Of the 61 patients in whom no pain was present at any time, 48 (78.7%) were noted to have moderate or severe hemorrhage. Likewise, of the 11 patients who obtained relief of pain with the onset of bleeding, 7 (63.6%) were in the moderate and severe groups. On the other hand, 41 (68.3%) of the 60 pa-

TABLE 3.—*Relationship of Pain to Severity of Bleeding*

Severity of Hemorrhage	Pain Present: Relieved by Bleeding, No.	Not Relieved by Bleeding, No.	Increased with Bleeding, No.	Pain Not Present: Not Indicated, No.	Never Present, No.
Minimal	4	41	9	19	13
Moderate	6	14	2	8	20
Severe	1	5	0	3	18
Total	11	60	11	30	61

tients who did not obtain relief of pain with the onset of bleeding were in the minimal hemorrhage group, whereas only 19 (31.7%) had moderate or severe bleeding. (The reliability of the percentages compared above was determined as difference [%] divided by standard error of difference [%], or $44 \div 7.8 = 5.6$; because the difference is 5.6 times its standard error, it is reliable and cannot be at-

tributed to chance alone.) In this series the continued presence or exaggeration of ulcer pain suggested minimal bleeding and the relief of pain suggested more severe bleeding. Thus, historical information in regard to the ulcer pain pattern and the onset of bleeding in duodenal ulcer disease can be used to distinct advantage in the clinical evaluation of the severity of hemorrhage.

The high familial incidence of duodenal ulcer and the significantly greater occurrence of blood group O among patients with duodenal ulcer favors the theory that certain hereditary factors may be involved in susceptibility to this disease. It has been suggested that the inheritance of blood group O is related to the absence of some local protective agent or the presence of some ulcerogenic agent.

TABLE 4.—*Distribution of Blood Groups*

Author	Group	Blood Group O No.	O %	A No.	A %	B No.	B %	AB No.	AB %
Hervey, G. W., and others: J. A. M. A. 165:80-81 (Jan. 18) 1957	Control	64,581	45.6	57,807	40.8	14,115	10.0	5,271	3.7
Aird and others [7c]	Control	4,578	47.0	4,219	41.0	880	9.0	313	3.0
Buckwalter and others [7b]	Control	2,892	45.8	2,625	41.6	570	9.0	226	3.6
Aird and others [7c]	Duodenal ulcer	1,048	56.6	616	33.3	141	7.6	46	2.5
Buckwalter and others [7b]	Duodenal ulcer	698	53.7	472	36.3	102	7.8	29	2.2
Present study	Duodenal ulcer	61	59.8	21	20.4	9	8.8	1	0.9

ABO Blood Groups

The relationship of ABO blood groups to various diseases has come into focus recently. Interest has been especially centered on those conditions associated with changes in gastric acidity, e. g., duodenal and gastric ulcers, pernicious anemia, and gastric carcinoma. Many authors [7] have reported that there appears to be an increased frequency in the incidence of blood group O in patients with duodenal ulcer as compared to control subjects.

In the present study of 162 patients with bleeding duodenal ulcer, only 102 had their blood typed. It must be presumed that only those bleeders who, in the opinion of their attending physicians, might require transfusions were typed. The 102 patients, therefore, probably represent those with more severe bleeding. Table 4 demonstrates the distribution of the blood types and compares them with previously reported findings in controls and in patients with duodenal ulcer from the United States and England. There appears to be an increased frequency in the incidence of blood group O among the patients with bleeding duodenal ulcer who comprise this study and a decreased incidence of blood group A.

TABLE 5.—*Relationship of Season to Severity of Bleeding*

	Incidence, No.		Severity: Minimal No.	Minimal %	Moderate and Severe No.	Moderate and Severe %
January	17					
February	17	54	21	38.8	33	61.0
March	20					
April	10					
May	7	29	17	58.6	12	41.4
June	12					
July	16					
August	9	37	23	62.1	14	37.8
September	12					
October	19					
November	11	42	16	38.1	26	61.8
December	12					

Monthly and Seasonal Incidence

The increased incidence of activation of duodenal ulcer disease in the fall and spring months has long been noted. Boles and Westerman [8] commented on the increased occurrence of bleeding from duodenal ulcers in the fall and winter. In the present series also, a higher incidence of bleeding occurred in the fall and winter months, with a relative lull in the spring (table 5). The peak months were March and October, with 20 and 19 cases of bleeding respectively.

In comparing the severity of bleeding with the various seasons of the year, the fall and winter likewise had a greater proportion of those with moderate and severe bleeding (61.0% and 61.8%) than did the spring and summer (41.4% and 37.8%).

Summary and Conclusions

In a series of 162 consecutive cases of bleeding duodenal ulcer, the continued presence or exaggeration of pain compatible with duodenal ulcer disease was associated with minimal bleeding, whereas relief of pain was more characteristic of moderate and severe hemorrhage. Hematemesis by itself was not found to be a clear-cut indication of severe bleeding. Syncope, on the other hand, commonly heralded a massive hemorrhage. A history of upper gastrointestinal hemorrhage was of no apparent value in predicting the severity of bleeding from duodenal ulcer. The proportion of the number of severe hemorrhages to the total number of cases for a given decade increased progressively with advancing age. There appeared to be an increased frequency in the incidence of blood group O among patients with bleeding duodenal ulcer. An increased occurrence and severity of bleeding in the fall and winter months was also noted.

These findings suggest that greater stress should be placed on the pain pattern in patients with bleeding duodenal ulcers. The "silent bleeder" or the one

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in whom ulcer pain has been relieved with bleeding would be more likely to have a more severe hemorrhage and, therefore, would demand a more vigorous therapeutic approach.

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The opinions and assertions expressed herein are the private ones of the authors and are not to be construed as official or representative of the United States Navy.

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APPENDICEAL-VESICAL FISTULA

UNCOMMON COMPLICATION OF ACUTE PERFORATIVE APPENDICITIS WITH REPORT OF THREE CASES

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Acute pelvic appendicitis which creates the appendiceal-vesical fistula is one of the commonest unrecognized forms of acute appendicitis. Fistula results from adhesion of the distal end of the appendix to the bladder wall, abscess formation, and rupture into the bladder. Diagnosis is made by a history of passage of gas and feces into the urine, rectal frequency and urgency, and the finding of tenderness in the pelvis on digital rectal examination. Appendiceal-vesical fistula is rare, 41 cases having been mentioned in the world's literature, with three more reported here. There is a predominance of males with this lesion.

Appendiceal-vesical fistula is caused by adherence of the distal end of an inflamed pelvic appendix to the urinary bladder wall, with perforation, abscess formation, and finally rupture of the abscess into the bladder. This complication of acute pelvic appendicitis is uncommon. Parton [1] surveyed the world literature on this subject, was able to gather 40 cases reported since 1898, and documented an additional case.

Appendiceal-vesical fistula is usually not diagnosed prior to operation. The clinical findings consist of a variety of gastrointestinal and genitourinary complaints which appear shortly after an unrecognized attack of acute pelvic appendicitis. Often the patient is treated symptomatically for such complaints for months or years before the true nature of the illness is discovered.

Our discovery of three patients with appendiceal-vesical fistulas within a short period of time impressed us with the still important problem of acute perforative appendicitis. Myer,[2] with extensive experience with abdominal surgery in acute cases at Cook County Hospital, Chicago, declared that physicians have become complacent about acute appendicitis in interest in more exotic surgery and urged that the menace of acute appendicitis be reemphasized to medical students, the medical profession, and public. Acute appendicitis is still an important cause of morbidity and death. In the year 1955, approximately 5,000 deaths from this disease were recorded in the United States.[3] Cantrell and Stafford [4] stated that the residual mortality from acute appendicitis is determined by the incidence of perforation, since acute appendicitis without perforation carries virtually no mortality. The ultimate elimina-

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tion of acute appendicitis as a cause of mortality lies in the early recognition of the disease and its complications and prompt surgical procedure.

Report of Cases

CASE 1.—A 12-year-old boy with a history of chronic chest illness with productive cough and wheezing had been underweight since age 6. Eight

Fig. 1 (case 1).—Film taken 24 hours after barium enema was given, showing fistula between cecum and bladder.

months prior to his visit, the mother stated that the boy had complained of bouts of diarrhea, lower abdominal pain, fever, and frequency and burning on urination. Shortly thereafter the mother noted pus and gas in his urine.

Physical examination revealed an undernourished, emaciated boy who weighed 55 lb. (24.9 kg.) and was 5 ft. 1 in. (154.9 cm.) tall. There were numerous fine crepitant rales throughout both lungs. The abdomen was slightly distended, with tenderness in both lower quadrants. Proctoscopic examination did not show any abnormalities. Urine samples examined on numerous occasions were cloudy with a heavy sediment of pus cells and some red blood cells. X-rays of the stomach and small intestine were reported as showing normal results. An x-ray of the colon showed a questionable filling defect in the cecum. A follow-up abdominal film taken 24 hours later showed a fistula into the bladder (fig. 1).

At surgery, the cecum was found adherent to the dome of the urinary bladder. The stump of the appendix and a 0.5-in. long fistula between the cecum and the bladder were present. Evidently, this cecovesical fistula had occurred after an episode of acute appendicitis, complicated by appendiceal abscess with perforation into the bladder. The stump of the appendix measured approximately 1 cm. in length. On microscopic examination, the appendix revealed extensive fibroplasia with many new-formed vessels surrounded by a mild round and plasmacytic exudation.

CASE 2.—A 40-year-old man became ill two and one-half years prior to his visit to Cook County Hospital with symptoms of lower abdominal pain, diarrhea, chills, and fever. One month later a painful swelling developed in his right buttock. Two months later he noted hematuria, pyuria, and frequency of urination. He developed progressive anorexia, weight loss, and weakness. At about this time he developed another painful abscess in his right inguinal region. He was hospitalized in another hospital where an intravenous pyelogram showed hydronephrosis on the right and a filling defect in the right side of the urinary bladder which were interpreted as compatible with a chronic inflammatory process, probably tuberculosis (fig. 2). For this, the patient was treated with antituberculosis therapy for six months, and finally a nephrectomy on the right was performed in September, 1956. The pathology report on the surgical specimen gave a diagnosis of chronic pyelonephritis and hydroureter due to obstruction. The patient, how-

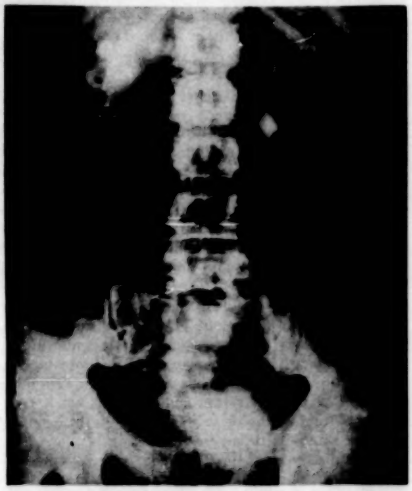

Fig. 2 (case 2).—Pyelogram showing pyelonephritis on right and hydronephrosis with filling defect in right side of urinary bladder.

ever, continued to have symptoms of sepsis, and the urine remained turbid and loaded with red and white blood cells.

He was admitted to the Cook County Hospital in May, 1957. Additional information included a history of passing gas through the urethra and through

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the two abscesses. On physical examination the patient was severely emaciated. Two draining fistulas were present, one over the right iliac crest and the other over the right buttock from which drained a bloody purulent material with occasional puffs of gas. Liver and spleen were both palpable. Blood examination revealed a hemoglobin level of 63 Gm. % and red blood cell count of 3,830,000 per cubic millimeter. The total blood protein level was 6.1 Gm. %, with albumin level of 3.9 and globulin level of 2.2 Gm. %.

On cystoscopy, the bladder mucosa was hyperemic and above the right ureteral orifice there was a suggestion of a fistula. A cystogram was not diagnostic. Escherichia coli organisms were cultured from the urine.

Barium enema showed a number of irregular fistulous tracts extending from the ileocecal region toward the gluteal area. A study of the small intestine showed a narrow, irregular segment of lower ileum with fistulous tracts (fig. 3). A preoperative diagnosis was made of regional ileitis with perforations or appendiceal-fistula after perforated appendix.

An exploratory laparotomy was done in June, 1957. A mass in the right lateral pelvic wall involving the appendix and terminal ileum was found. This mass compressed the right ureter, thus accounting for the right hydronephrosis. The tip of the appendix was attached to the right base of the bladder, and its middle third was over the right ureter. There was a fistula between the appendix and the bladder. There were also two fistulous communications—one between the terminal ileum and the granulomatous mass over the right external pelvic wall and another between the mass and the skin over the right hip. No evidence of regional enteritis,

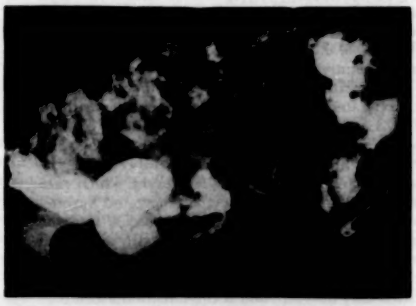

Fig. 3 (case 2).—Study of small intestine showing narrow irregular segment of lower part of ileum, with fistulous tracts.

colitis, or disease of the small intestine was found. The surgeon (N. J. C.) stated that all the pathology was secondary to acute appendicitis and abscess formation. The loops of the terminal ileum were freed, and the openings in the intestine were closed. The fistula in the right base of the bladder was closed, and the appendix was removed.

The histological examination of the appendix showed severe acute inflammatory cell infiltration of all the layers with severe edema and congestion

Fig. 4 (case 3).—Barium enema through transverse colostomy, showing appendiceal-vesical and sigmoid-vesical fistulas.

of the entire wall. Postoperatively the patient recuperated rapidly. The urine cleared, the cutaneous sinuses closed, and the patient gained weight. He was discharged 18 days after the operation. Since that time the patient has gained 30 lb. (13.6 kg.) in weight and has returned to work for the first time since onset of illness.

Case 3.—The patient was operated on for bladder stones at the age of 12 years. In 1941, at the age of 32, he developed an inflammation of the lower intestine, after which he noted that feces and pus appeared in his urine. A diagnosis of sigmoid-vesical fistula was made, and a midtransverse colostomy was performed in 1941. His urinary difficulties disappeared, and he did not return for any additional definitive surgery for 17 years. He entered Cook County Hospital on June 6, 1958, because of recurrence of his attacks of urinary discomfort with feces and pus in his urine. There were no chills and fever. These symptoms were present for 10 weeks prior to admission. There was also a history of an acute episode of lower abdominal pain about four months prior to entrance, which the patient disregarded.

On physical examination, the patient was well nourished. The abdomen was rounded and obese. There was a transverse suprapubic scar and a right inguinal scar. There was a double-barreled colostomy in the midtransverse colon which was discharging liquid fecal matter. The rectal canal was

strictured so that the finger could not be inserted. Laboratory examination revealed that the urine was cloudy, with albumin 1+ with many white and red blood cells. The hemoglobin level was 16 Gm. %. Chemical investigation revealed that urea, sugar, cholesterol, total protein, calcium, and alkaline phosphatase levels were normal. An intravenous pyelogram revealed good function bilaterally, and both ureters were visualized and appeared normal. The bladder appeared irregular, however, and there was a suggestion of contrast material outside the bladder wall. An x-ray of the colon through the transverse colostomy showed an appendiceal-vesical fistula and the old sigmoid-vesical fistula (fig. 4). Cystoscopy revealed a markedly contracted bladder with blood and feces in the urine.

At operation, a patent appendiceal-vesical fistula was found. Appendectomy and closure of the bladder and intestinal fistulas were performed. The sigmoid-vesical fistula was present as a thin fibrous strand which was removed. The gross pathological specimen consisted of a piece of light brown soft tissue, 4 cm. in length, with a fistulous tract measuring 1.6 cm. in length, which easily admitted a 2-mm. probe. Microscopic section revealed a cross-section of appendiceal wall with moderate thickening of the wall and infiltration by chronic inflammatory cells. The diagnosis was chronic appendicitis. The patient's urinary difficulties cleared, and he made an uneventful recovery.

Comment

Acute pelvic appendicitis which creates the appendiceal-vesical fistula is one of the commonly unrecognized forms of acute appendicitis. The classic type of acute appendicitis starts with generalized abdominal pain, which later localizes in the right lower quadrant, associated with fever, nausea, vomiting, and tenderness in the right lower quadrant of the abdomen, and is commonly recognized. However, as Meyer and associates[5] pointed out some years ago, when these initial symptoms of acute appendicitis are present without later right lower quadrant localization, then one must consider an acute pelvic appendicitis. The diagnosis is made by considering this possibility and finding tenderness in the pelvis on digital rectal examination. When the patient also complains of diarrhea which is actually rectal frequency and urgency, then the diagnosis of pelvic appendicitis or abscess is certain.

Perforation of the appendix during acute pelvic appendicitis and the formation of an abscess is not unusual. The wall of such an abscess includes, in part or in combination, the appendix, omentum, coils of small intestine, and parietal peritoneum. In addition, a hollow viscus such as the cecum, sigmoid, rectum, urinary bladder, or female genital organs may form part of the wall of the abscess, depending on its location. Usually the deep abscess presents or spontaneously ruptures into the sigmoid colon, rectum, or posterior vaginal fornix.

Uncommonly the pelvic abscess ruptures into the urinary bladder. This is due to a low-lying cecum or an unusually long appendix which is located in the pelvis and adjacent to the bladder. The inflamed appendix becomes adherent to the urinary bladder, causing secondary inflammation of the bladder wall. As the inflammation progresses to the stage of abscess formation, there is a rupture through into the bladder, with the formation of an appendiceal-vesical fistula. It is important to remember that adherence of the appendix to the bladder precedes fistula formation. The fistula is not simply the result of perforation of a pelvic appendiceal abscess into the bladder, as such an abscess is much more likely to rupture into the rectum than into a thick-walled viscus such as the bladder.

The three patients reported were males. There is a predominance of males with appendiceal-vesical fistula, since the interposition of the uterus and female adnexa between the bladder and the intestine prevents this complication in women.

The symptoms of appendiceal-vesical fistula are variable and may include (1) gastrointestinal complaints which are consistent with acute pelvic appendicitis in early stages and vague abdominal pain and diarrhea in late stages, (2) urinary symptoms which vary from those of a mild infection to those of a marked cystitis with feces and gas in urine, and (3) chronicity, measured in months or years, because the condition is not recognized.

Symptoms, signs, or history of the primary causative disease, acute pelvic appendicitis, as often happens, were not present in our patients, and the cause of illness was suspected only after complete gastrointestinal and urologic studies.

Two of our patients, in cases 1 and 3, had gastrointestinal symptoms of diarrhea and lower abdominal pain in addition to urinary complaints. Symptoms referable only to the urinary bladder, however, may be the presenting complaints and may completely mask the intestinal pathology. Our second patient was ill for two and one-half years with predominantly urinary symptoms and sepsis so that he was treated for urinary tract tuberculosis and later operated on for hydronephrotic kidney without relief. Lazarus and Marks[6] described the bladder involvement early in the development of the fistula when the appendiceal abscess is adherent to the bladder. Here a pericystitis is present which produce symptoms of frequency, urgency, and burning on urination. The rupture of the abscess into the bladder may be explosive at onset with additional symptoms of acute cystitis such as severe tenesmus, strangury, pyuria, and albuminuria. Later a chronic cystitis may develop, and if the infection ascends to the kidney, the picture is further complicated by an acute pyelonephritis with chills, fevers, and lumbar pain. A chronic pyelonephritis may then follow, as was present in our second patient, and the urine may continuously contain pus cells, red blood cells, casts, albumin, bacteria, and occasionally gross blood.

The illness is usually chronic. Patients may complain of gastrointestinal and/or urinary symptoms for months or years. Mayo and Blunt[7] noted an average duration of symptoms of 18.5 months in 48 patients with intestinal-vesical fistulas before they were recognized. Our first patient had symptoms for eight months, the second for two and one-half years, and the third for 10 weeks before their illness was recognized.

The laboratory may make the definite diagnosis. Barium enema studies identified the fistulas in two of our patients. The first patient urinated barium given by colon enema, and x-ray showed barium in the urethra (fig. 1). The fistula was visualized in our third patient after x-ray of the colon (fig. 4). Since urinary signs and symptoms are a prominent part of this illness, cystoscopy may be of value in establishing the diagnosis. During the early stages, there is a localized area of cystitis. The actual fistulous opening is rarely identified, however, because of the marked inflammatory changes and bullous edema. A cystogram or, occasionally, the installation of a contrast medium, such as methylene blue or indigo carmine, into the bladder and subsequent recovery of the medium in the stool, may prove the diagnosis. A history suggestive of acute pelvic appendicitis prior to the onset of urinary symptoms, with gas and feces in urine, should alert one to the possibility of an appendiceal-vesical fistula which may be identified by gastrointestinal and urologic studies.

Summary

Appendiceal-vesical fistula is rare, 41 cases having been mentioned in the world's literature. Three more are reported here. The causative lesion is acute pelvic appendicitis with adhesion of the distal end of the appendix to the bladder wall, abscess formation, and rupture into the bladder. This diagnostic possibility should be kept in mind when patients have a history of gastrointestinal and urinary complaints combined with the passage of gas and feces in the urine.

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CLINICAL NOTES

BISHYDROXYCOUMARIN TOXICITY

SOME PHYSIOLOGICAL ASPECTS AND REPORT OF A DEATH FROM SPONTANEOUS SUBDURAL HEMATOMA

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An increasing number of deaths have been attributed to hemorrhagic diathesis complicating bishydroxycoumarin (Dicumarol) therapy. Since its introduction to clinical use in 1941, a variety of indications have been described for the use of orally given anticoagulants.[1] These include nonfatal pulmonary embolism, primary and postoperative phlebothrombosis and thrombophlebitis, sudden embolic or thrombic arterial occlusion, postoperative venous thrombosis or embolism, and myocardial infarction.

The hazards of anticoagulation have also been emphasized. Duff and Shull,[2] in their review of the first 23 fatalities due to bishydroxycoumarin therapy, summarized the most commonly encountered contraindications. Significant hepatic or renal insufficiency leads their list. Included, too, are ulcerative lesions of the gastrointestinal tract, blood dyscrasias with associated bleeding tendencies, subacute bacterial endocarditis, threatened and incomplete abortions, and obstetric cases near term.

Historical Background

The basic investigations of Solandt and others[3] paved the way for the current widespread use of anticoagulants in the treatment of myocardial infarction. In 1938, using a highly purified heparin preparation, they were able to prevent the formation of mural thrombi after the experimental production of myocardial infarctions in dogs. Wright,[4] in 1949, published a three-year study of 800 patients at 16 separate hospitals, half of whom were treated with anticoagulants after established myocardial infarctions. Analysis revealed a reduction of the death rate by one-third, and of the thromboembolic

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complications by one-half, with the prolonged use of bishydroxycoumarin. Since that time thousands of cardiac patients, many of whom have varying degrees of hepatic and renal insufficiency, have been placed on therapy with anticoagulants.

It is the intention of this report to reemphasize the dangers of anticoagulation in the ambulatory patient after myocardial infarction, notably in the presence of incipient or frank congestive heart failure, and to present the first case report of a death from spontaneous subdural hematoma in a patient receiving bishydroxycoumarin.

Report of a Case

A 58-year-old man entered the emergency ward of the Peter Bent Brigham Hospital at 3 a. m. complaining of shortness of breath and rattling in his chest of one day's duration. Approximately 24 hours prior to admission the patient awakened out of a sound slumber with symptoms which persisted through the night, preventing further sleep. His symptoms lessened during the next day but returned again the evening of admission. About four hours after retiring the patient was again awakened, this time with a "splitting" suboccipital and frontal headache. He denied nausea, vomiting, dizziness, vertigo, tinnitus, or weakness. There was no chest pain, history of bleeding tendency, or previous ankle edema. He was admitted to the overnight ward for study.

History.—The patient had first been seen at the Peter Bent Brigham Hospital in 1953 for complaints of substernal pain. Serial electrocardiograms at that time demonstrated posterior myocardial infarction, and he was treated with bed rest and anticoagulation therapy with bishydroxycoumarin. His recovery was uneventful, and he did well for the next four years, returning to work and being almost completely free of symptoms. On occasion he required a nitroglycerin tablet for angina but took only 50 tablets in 48 months.

His second admission, in March, 1957, was for increase in frequency and severity of his anginal attacks. An electrocardiogram demonstrated an intramural myocardial infarction. During this admission a fasting blood sugar level was noted to be elevated and a glucose tolerance test result was consistent with mild diabetes mellitus. Laboratory data during that stay were as follows: hematocrit value 47%; white blood cell count 8,000 per cubic millimeter, with normal differential count; blood urea nitrogen level 13 mg. per 100 cc.; total serum protein level 5.8 Gm. per 100 cc.; alkaline phosphatase level 3.2 units per 100 cc.; thymol turbidity 14 units; serum bilirubin level 0.52 mg. per 100 cc.; sedimentation rate 32, corrected to 22 mm. per hour (Westergren method); protein-bound iodine level 7.2 mcg. per 100 cc.; and lactic dehydrogenase level 130 units (normal 100). The prothrombin time was 78% of normal on admission. The patient was discharged with diagnoses of coronary artery disease, mild diabetes mellitus, mild congestive heart failure, intramural myocardial infarction, and peripheral arteriosclerosis.

Medication at discharge included bishydroxycoumarin, 50 mg. orally four times daily. Two days after discharge he returned to the outpatient department with a complaint of spontaneous nosebleed. His prothrombin time was noted to be 21% of normal, and there was no evidence of gross or occult bleeding in his stools. He was therefore continued on therapy with the same dosage of bishydroxycoumarin, and his prothrombin time was checked weekly. He was not bothered with further bleeding, and the prothrombin times varied between 70% and 10.5% during the ensuing 10 weeks up to the time of his last admission.

Hospital Course.—On the patient's admission to the emergency ward, physical examination revealed the following pertinent findings: His blood pressure was 115/80 mm. Hg; pulse 96 per minute; temperature 98.0 F (36.7 C); and respirations 20 per minute. His fundi were pale and showed evidence of old chorioretinitis. His disks were unremarkable. His mouth and throat were normal. His neck veins were not distended in the recumbent position, but his chest was noted on auscultation to have moist and bubbling rales up to the midback bilaterally. There was no evidence of consolidation. His heart was not enlarged to percussion.

A grade 3, poorly transmitted, apical diastolic murmur was heard. His abdominal findings were unremarkable. One-plus edema of the ankles was noted. An electrocardiogram, compared with his previous tracings, showed no important changes. A diagnosis of headache, caused by chloral hydrate, and mild congestive heart failure was made. Bed rest was prescribed, and it was planned to reevaluate his condition in the morning.

At 6:45 a. m., about three and one-half hours after the admission, the house officer was informed that the patient was unresponsive. Repeat physical examination revealed an eccentrically dilated and fixed right pupil, absent corneal reflexes, and flaccidity of the left side of the body, including the face. There was no response to painful stimuli. A bilateral Babinski sign as well as diminished left-sided deep tendon reflexes were noted. A diagnosis of primary intracranial hemorrhage was made and the neurosurgical service called.

Because of the rapid deterioration of his condition, he was taken immediately to the operating room and bilateral frontal and right temporal bur holes were made with the patient under local anesthesia. Blood studies done preoperatively but reported postoperatively revealed a prothrombin time of 8%. At operation approximately 100 cc. of clotted fresh blood and serum was found in the subdural space over the right temporal region. This was removed by through-and-through irrigation (between

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the bur holes). The patient appeared to have withstood the procedure well but did not regain consciousness. Because of the brisk bleeding encountered from the small scalp and dural incisions, the patient received 50 mg. of phytonadione (Mephyton) intravenously, two units of whole blood, and two units of plasma. Postoperatively, there having been no evidence of pulmonary congestion, no digitalis was administered. He received 100 cc. of 50% glucose solution every eight hours for control of cerebral edema; gastric and bladder drainage were done. Immediately after operation his vital signs were as follows: blood pressure 110/80 mm. Hg; temperature 104 F (40 C); and Cheyne-Stokes respiration present.

The remainder of the patient's postoperative course was downhill. His temperature hovered about 101 F (38.3 C); his pupils varied in size on occasion, his right pupil dilating to midposition. His prothrombin time rose, with phytonadione supplement, to 40% nine hours postoperatively, to 80% 24 hours later, and 100% in three days. On his fourth postoperative day he again developed pulmonary edema and was digitalized. He never regained consciousness, and on his fifth postoperative day, his respirations ceasing before his heartbeat, he died.

Postmortem findings revealed approximately 5 cc. of clotted blood at the operative site subdurally, evidence of inactive rheumatic heart disease with mitral stenosis, and coronary artery disease. No evidence of intracerebral hemorrhage was noted, though the brain was moderately edematous.

Comment

In the absence of a history of trauma, and in view of the apparent freshness of the subdural clot found at time of surgery, this case appears to represent spontaneous hemorrhage and death due to bishydroxycoumarin toxicity. While there have been a number of fatalities due to use of bishydroxycoumarin secondary to intracranial hemorrhage, these have been reported as due to cerebral vascular accidents. A search of the literature reveals no previous report of a case in which the fatal diathesis was limited to the subdural space.

A provoking observation in this patient's course is that he was, by history and clinical evaluation, in acute congestive heart failure for at least 24 hours prior to his admission. Powers,[2] in 1950, reported two deaths as a complication of bishydroxycoumarin therapy, both patients having congestive heart failure and icterus. He suggested two factors in the apparent excessive activity of the anticoagulant. Chronic passive congestion of the liver interfered with the formation of prothrombin to the extent that administration of what had previously been safe doses so severely disrupted the coagulation mechanism as to cause hemorrhage. The possibility that diminished renal filtration due to congestive failure caused retention of bishydroxycoumarin, with subsequent toxicity, was also offered. Numerous studies have substantiated a decreased ability of the liver to utilize vitamin K in the presence of chronic passive congestion, and while most researches have demonstrated that the renal excretion of bishydroxycoumarin as such is negligible, Butler and James [4] reported a case of death due to hemorrhage in a patient in acute renal failure while on bishydroxycoumarin therapy.

In the patient reported here, studies less than two months prior to the terminal episode demonstrated normal liver function, and the response to phytonadione postoperatively indicated a normal capacity with sufficient stimulus to produce prothrombin. At the time of the patient's admission to the hospital, however, his prothrombin time was 8%. This, therefore, is the picture of a normotensive patient after myocardial infarction, on constant therapy with bishydroxycoumarin, with previously normal liver function, who sustained a fatal hemorrhage coincident with an episode of acute congestive heart failure. These observations are interpreted as lending indirect support to Powers' [2] hypotheses.

The variation in response to similar doses of anticoagulants among different patients, and in the same patient at different times, is well known, and there is little doubt that some of the factors delineated above explain these in part. Still, an understanding of bishydroxycoumarin toxicity is at present incomplete.

Conclusions

It should be emphasized that the cardiac patient in mild congestive heart failure is likely to be particularly sensitive to the effects of bishydroxycoumarin. While the precise mechanism of this sensitivity is not clear, there is increasing indirect evidence that transient alterations in liver and renal reserve, as in acute increase in congestive failure, may be sufficient to tip the balance. The importance of these considerations becomes apparent when one realizes the large number of patients which can be placed in this category.

Addendum

Since completion of this paper, Nathanson and associates have reported a death under similar circumstances in the *Annals of Internal Medicine* (49:1368-1372 [Dec.] 1958).

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INCARCERATED FEMORAL HERNIA CONTAINING AN OVARY

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The presence of an ovary in an inguinal hernia is not an uncommon occurrence, with or without strangulation; however, no previous record has been found of an ovary in a femoral hernia.

Report of a Case

A 43-year-old woman entered St. Luke's Hospital on April 29, 1959, complaining of abdominal pain of four days' duration. She had been moving a chair about her home on the day of initial symptoms and later noted the rather rapid onset of a severe, deep, somewhat constant midabdominal pain which radiated slightly above and mostly below the umbilicus. This was soon followed by nausea and vomiting, and the pain was more or less steady in intensity. During the next two days she remained bedfast, vomiting all ingested liquids; she also noticed the development of a tender mass in the right part of the groin. The day previous to admission she was able, however, to tolerate orally taken fluids.

History.—The history was significant in that, while caring for her invalid mother three years previously, the patient had noted the development of a mass in the right part of the groin, occasionally associated with lifting and disappearing spontaneously. On two occasions in the six months previous to this admission, she had experienced some slight midabdominal pain, similar to her present complaint, which spontaneously subsided. Except for irregular menses in the recent months her history was not remarkable.

Physical examination on admission revealed a slightly dehydrated woman in some distress with abdominal pain. Her temperature was 37.2 C (99 F), pulse rate 100 per minute, and respirations 20 per minute. Significant findings were limited to the abdominal and inguinal areas. The abdomen was slightly distended, peristalsis was present, and there was direct and rebound tenderness as well as suprapubic tenderness in both lower quadrants. Pelvic examination revealed also bilateral pelvic tenderness, and in the right part of the groin there was a 6-by-8-by-3-cm. somewhat fusiform mass parallel and overlying the inguinal ligament. It was markedly tender to touch. Roentgenograms revealed multiple gas-filled loops of small intestine in the upper and middle parts of the abdomen with several fluid levels, and it was felt that an early or incomplete mechanical intestinal obstruction was present. The white blood cell count was 14,600 per cubic millimeter, with 81% neutrophils and 1% nonfilamented cells; the hemoglobin level was 13.6 Gm. per 100 cc.; and the packed cell volume was 44 cu. cm. per 100 cc. of blood. Urine findings were not remarkable.

Operative Report.—The preoperative diagnosis was strangulated femoral hernia on the right. After the customary preparation, an incision was made parallel to the inguinal ligament on the right over the dome of the easily visible tumor which lay just below the inguinal ligament. Under deep layers of superficial fasciae was encountered the dome of this hernial mass which was easily separated from surrounding fat by blunt finger dissection; It was bluish and cystic in appearance and had a narrow, slender pedicle which had come through the femoral canal below the inguinal ligament. During manipulation the surface layers of this mass ruptured and clear fluid escaped from one of the two cystic areas. At the base of the space occupied by the fluid could be recognized tissue typical of corpus luteum; the specimen in hand was therefore ovary. The other cyst was ruptured intentionally and similar ovarian tissue noted.

It was impossible to reinsert the ovary under the inguinal ligament; consequently, the medial end of the inguinal ligament was divided and the pedicle of the ovary brought into the inguinal area. When the peritoneum was divided, a finger was passed down along the smooth, thick, broad ligament, and the anterior surface of the body of the uterus was palpated, which in addition carried a small fibroma. Although there were two fairly large cystic areas in this ovary, the remainder of the structure

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appeared reasonably normal and there seemed to be no reason to remove the ovary; the ovary was reinserted into the abdominal cavity. The femoral canal was closed, the inguinal ligament repaired, and the wound closed in layers. The patient made an uncomplicated recovery.

Comment

It is interesting to speculate on the occurrence of this condition. Obviously the ovary must have come through the femoral canal at a time when it was very small, since the femoral canal was of customary size, probably the diameter of a pencil. It would therefore appear that this must have taken place during the prepubescent period. The occasional apparent increase in size noted by the patient was undoubtedly due to the occurrence or subsidence of fluid in the hernial sac, although the normal-sized ovary should have been felt by the patient long before.

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DELAYED HEMORRHAGE AFTER PERCUTANEOUS KIDNEY BIOPSY

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and
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A case of delayed hemorrhage from the kidney after a percutaneous renal biopsy occurred on the ninth day after the diagnostic procedure and required an emergency nephrectomy.

Report of a Case

A 41-year-old man was admitted to the Metropolitan Hospital because a preemployment chest x-ray showed bilateral pleural effusions. Two weeks earlier the patient had experienced the onset of nocturnal orthopnea. There had been no chills, fever, or night sweats.

The patient had been essentially well until nine months prior to admission, when he developed lymphadenopathy, muscular weakness, and a wasting of the muscles of the lower extremities. A diagnosis of Guillain-Barré syndrome was made and the patient treated at another hospital with cortisone and physiotherapy. During this four-month hospitalization and the subsequent four-month follow-up, the patient had no hypertension or abnormal urinary findings. One month prior to his admission to Metropolitan Hospital his blood pressure was normal, but for the first time a trace of albumin was found in the urine. There was no history of epilepsy, diabetes, hypertension, or tuberculosis.

The patient was a well-developed, thin man in no acute or chronic distress. The physical examination showed a blood pressure of 180/110 mm. Hg and a pulse of 110 per minute. The positive physical findings were limited to arteriovenous nicking in both retinas, lymphadenopathy of the anterior cervical and inguinal nodes, and dulness to percussion at the base of both lungs posteriorly. There were diminished breath sounds and rales in the right lung base posteriorly. The liver edge was palpated 1 cm. below the right costal margin, and there was 2 + pitting edema of the ankles. Neurological examination showed a lack of sensation below the knees; absence of the abdominal, knee, and ankle reflexes; and wasting of the calf muscles, with a bilateral foot drop.

At the time of his admission, the urine showed a specific gravity of 1.015, 4 + albumin, no sugar, and no white or red blood cells. The hemoglobin level was 12 Gm. per 100 ml., the white blood cell count 16,900 per cubic millimeter, and the sedimentation rate 30 mm. per hour (Westergren method). The blood urea nitrogen level was 9 mg. per 100 ml., the transaminase level 22 units, the cholesterol level 220 units, and the total protein level 5.6 Gm. per 100 ml. with an albumin-globulin ratio of 3.4:2.2. Electrocardiographic changes were compatible with myocarditis. Three lupus erythematosus cell preparations showed negative results. Two intravenous pyelograms showed poor function bilaterally without evidence of dilatation. The chest x-ray revealed moderate bilateral pleural effusions.

After the initial examination, a thoracentesis was performed on the right and 700 cc. of clear yellow fluid aspirated. The fluid was sterile and contained no malignant cells. A biopsy of an enlarged inguinal node revealed reticular hyperplasia. Because of persistent proteinuria and the recent onset of hypertension, it was felt that a percutaneous kidney biopsy would be of diagnostic value. A renal biopsy on the right, after the method of Muehrcke,[1]

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was performed. A 2-by-0.1-cm. core of tissue was easily removed. That evening the patient developed pain in the right flank severe enough to require sedation. However, by morning the pain had subsided. The core of kidney contained cortex and medulla. There was partial fibrosis of glomeruli,

Fig. 1.—Longitudinal section through right kidney showing area of hemorrhage. There is no blood in pelvis.

starting within the glomerular stalk, and a dilatation of the tubules, which were obstructed by protein casts. A urinalysis three days after the biopsy showed 4 to 8 red blood cells per high-power field.

The patient had no difficulty until noon of the ninth day after the biopsy, when he developed sudden, severe, right flank pain. The blood pressure fell from 172/105 mm. Hg to 70/50 mm. Hg, and the patient became cold and clammy. The hemoglobin level fell to 8.6 Gm. per 100 ml. Levarterenol (Levophed) bitartrate was given intravenously to maintain the blood pressure level. During the evening a definite fulness developed in the right flank. The blood pressure stabilized just above shock level, and a trial at conservative management was therefore instituted. For the next 12 hours, the right flank mass increased in size and the patient's general condition deteriorated.

After consultation with members of the department of urology, it was agreed that immediate exploration of the flank was imperative. At 3 p. m. the day after the acute episode, the patient was taken to the operating room. Blood transfusions were begun and the patient was intubated while awake. The skin, subcutaneous tissue, and muscle layers were infiltrated with procaine and the flank opened. When the transversalis muscle was split, a massive retroperitoneal hematoma was disclosed. General anesthesia was induced, and about 1,500 cc. of dark red, semiclotted blood was removed from around the kidney, right lateral paravertebral sulcus, and retroperitoneal area over the vena cava and aorta. As the kidney was being carefully dissected from the center of the hematoma, it became apparent that there was a 4-cm. cruciate tear in the capsule. The extensive hemorrhage had dissected under the entire capsule. Bright red blood gushed from a cruciate tear in the lateral border of the kidney itself. Because the patient's condition was precarious and the pedicle could not be isolated, a nephrectomy was quickly accomplished. After the kidney had been removed, the patient improved sufficiently to permit opening of the peritoneum. There was no blood in the peritoneal cavity, but the retroperitoneal hematoma surrounded the ascending colon and had dissected into the leaves of the small intestinal mesentery. Three large drains were placed in the wound, which was closed in layers.

Fig. 2.—Cross-section through area of hemorrhage. Glomeruli can be seen above in remaining parenchyma.

During the operation the patient received 2,000 cc. of blood. At the end of the operation the blood pressure was 130/70 mm. Hg, and it remained at this level throughout the postoperative period. The urine output was 300 ml. the first day,

1,200 ml. the second day, and 1,600 ml. the third day. Thereafter, the output remained at about 1,600 ml. per day. After removal of the Levin tube, a general, low-potassium diet was instituted gradually. The blood urea nitrogen level gradually rose to 80 mg. per 100 ml. on the sixth day after the operation. This was associated with a rise of the serum potassium level to 6.4 mEq. and a fall of the serum sodium level to 127 mEq. Cortisone therapy was started at a dosage of 200 mg. per day. The wound healed uneventfully. The blood urea nitrogen level remained elevated until the ninth day and then gradually fell to 17 mg. per 100 ml. on the 21st day. The cortisone dosage was tapered off over a five-day period.

Pathological examination of the kidney showed a 2-cm. tear in the lateral border midway between the upper and lower poles. On section, the tear was seen to extend down to but not include the pelvis (fig. 1). A large area of necrotic parenchyma surrounded the tear. There was an extensive subcapsular hematoma which was loosely applied to the surface of the kidney. Microscopic examination revealed changes compatible with lower nephron nephrosis and acute glomerulonephritis. No needle tract was evident (fig. 2).

The patient was discharged on the 23rd day after nephrectomy with normal blood chemistry, hemoglobin level, and white and red blood cell counts; however, he had lost one kidney, and the diagnosis of the basic condition was still not clear.

Comment

Until 1949, percutaneous needle biopsy of the kidney was considered too hazardous for general use. However, in that year Iversen[2] reported 215 such procedures without a serious complication, and in 1953, Dean[3] described the use of needle aspiration biopsies for the diagnosis of kidney tumors. Nevertheless, these techniques were seldom used until 1955, when Muehrcke and others[4] published a series of papers on the use of the percutaneous kidney biopsy. Since that time, many physicians have used such biopsies for the diagnosis and study of nephrosis, glomerulonephritis, and other kidney diseases. Though rarely reported, serious hemorrhage associated with the biopsy is an ever-present possibility. Muehrcke[1] states that hemorrhage has never been a problem, but he reports that of 100 consecutive patients, 96% had microscopic hematuria, 7% had gross hematuria, and in one the hematuria was such that the patient required transfusion.

Summary

A case of delayed bleeding occurring after a percutaneous biopsy of a kidney was unusual in that the patient did well and apparently had no ill-effects from the biopsy until the ninth day after the procedure, when he suddenly went into profound shock secondary to a delayed rupture of the kidney from which the biopsy specimen was taken. The resultant hemorrhage jeopardized the patient's life and necessitated an emergency nephrectomy. The renal biopsy is a recognized diagnostic procedure. However, the patient should be carefully observed for two weeks thereafter. As more biopsies are attempted, more such cases are likely to occur. An awareness of the possibility of delayed bleeding will facilitate its early diagnosis and treatment.

1901 First Ave. (29) (Dr. Felton).

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2. Iversen, P., and Brun, C.: Aspiration Biopsy of Kidney, Am. J. Med. 11:324-330 (Sept.) 1951.

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SHOULD PATIENTS BE HOSPITALIZED FOR PERORAL ENDOSCOPIC PROCEDURES?—We definitely do not hospitalize all patients for any of the 3 procedures with which we are concerned: direct laryngoscopy, bronchoscopy or esophagoscopy. . . . The patient is admitted if for any reason we plan to use general anesthesia. For diagnostic endoscopy we admit children almost always, because this permits better premedication and better control. In the anatomically difficult patient, the short, thick-necked individual, we generally admit the patient, especially for direct laryngoscopy, or esophagoscopy. The patient who is apprehensive and nervous can be much better managed if admitted and allowed to rest in bed before and after the procedure. Obviously, elderly and debilitated people should be admitted, as well as patients with fever or recent hemorrhage. As for foreign bodies, all depends on the nature and location of the foreign body, and more especially the patient's present condition. If there is any threat of dyspnea, of course the patient should be admitted.—C. L. Jackson, M.D., *The Annals of Otology, Rhinology & Laryngology*, June, 1959.

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. KAUTZ, M.D., *Secretary.*

OCCURRENCE OF SERIOUS BACTERIAL INFECTIONS SINCE INTRODUCTION OF ANTIBACTERIAL AGENTS

Maxwell Finland, M.D., Wilfred F. Jones Jr., M.D.
and
Mildred W. Barnes, M.S., Boston

The introduction and widespread use of chemotherapeutic and antibiotic agents has resulted in profound changes in the number and character of infections that are being encountered. Emphasis has been placed most recently on the number and seriousness of staphylococcic infections, particularly those occurring within hospitals. This has been brought strikingly into our consciousness because of the large number of outbreaks in nurseries and maternity wards and by the high incidence of infections in originally clean surgical wounds and as complications of debilitating diseases, events which have resulted in considerable morbidity and appreciable mortality within hospitals. There is also some evidence of extension of these infections into the communities. The problem has been recognized as being world-wide and extending to all areas where antibiotics have been extensively used. It has also been the subject of many conferences and of a number of monographs.[1]

Although the staphylococcus problem has received considerable attention and emphasis from many workers, a number of others have also become impressed recently with the increasing prevalence and seriousness of other groups of infections, particularly those of the coliform organisms. This term will be used loosely to include various aerobic gram-negative bacilli (other than the so-called enteric pathogens, namely the salmonellas, shigellas, and specific strains of Escherichia coli) that are usually considered to be normal constituents of the fecal flora, especially the common species of Escherichia, Klebsiella-Aerobacter, Alcaligenes, Proteus, and Pseudomonas. As with the staphylococcus, the concern about such infections has been due, in a large measure, to the fact that a major proportion of these organisms are relatively resistant in vitro to most of the widely available antibacterial agents and that the infections caused by them respond poorly to treatment with these drugs and are the cause of an increasing number of deaths. A few reports of cases of serious gram-negative bacillary infections, particularly those with bacteremia, have appeared during the last few years.[2] Some of these patients have demonstrated one particularly dramatic feature of these infections, namely bacteremic shock.[3]

In spite of these reports and of some general appreciation of these problems, there is a dearth of reliable information as to the incidence of staphylococcic infections, particularly with respect to their importance as a cause of serious disease and deaths since the introduction of modern antibacterial drugs.

Few, if any, of the numerous reports have dealt with the changes in the frequency with which serious and fatal infections with these and other bacteria are being encountered in the same hospitals since the advent of modern chemotherapeutic drugs. This may be due, in part, to the nature and general prevalence of these organisms and the fact that they are most frequently present in the absence of disease, and, in part, to the wide spectrum of infections which may be caused by each of these different organisms. These factors often make it difficult to determine their true significance when such organisms are grown in cultures from any given patient.

It would, of course, be of great interest to determine to what extent changes have taken place in the character of bacterial infections throughout the population. This is obviously impossible, not only because of the great difficulty in obtaining information about the bacterial etiology of infections on any appropriate scale outside of hospitals but also because there is no base line available for comparison with the current or recent status. Such information should be available in some hospitals.

The data presented in this paper were, therefore, gathered in response to this need for reliable information on the changing pattern of serious staphy-

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lococcic and other specific bacterial infections in relation to the use of the antimicrobial agents. They were collected at the Boston City Hospital where there has been a continuous interest in infectious disease antedating the introduction of the sulfonamides, and where there is available a large amount of bacteriological material carried out by the same competent and conscientious bacteriologists throughout the same period.

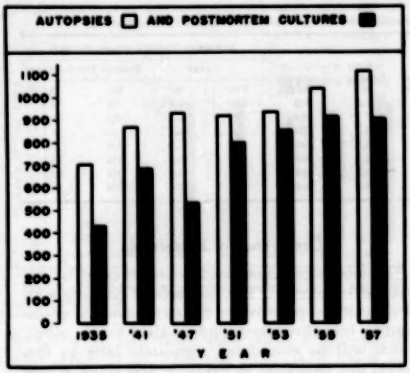

Fig. 1.—Autopsies performed and postmortem cultures made in selected years at Boston City Hospital.

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Methods and Limitations of Study

The large volume of material that was available necessitated limiting this survey to certain key years and to certain clearly defined entities. The following years were therefore chosen for the survey: 1935, the year before the introduction of sulfanilamide and its derivatives; 1941, after the sulfonamide drugs had achieved wide use and before penicillin became available; 1947, after penicillin and streptomycin had already been used widely and intensively and before the introduction of the broad-spectrum antibiotics; 1951, after some of the broad-spectrum antibiotics had already come into wide use and before the introduction of erythromycin and other antistaphylococcic antibiotics; and 1953, 1955, and 1957, in order to define recent trends after most or all of the currently available antibiotics had already been widely and extensively used.

In order to make valid comparisons and also to minimize errors in interpretation, as well as to limit the study still further, only the following entities were included: (1) autopsies in which satisfactory cultures were made and which yielded bacterial pathogens; (2) bacteremias (organisms grown from blood cultures); (3) meningitides (bacteria grown from cerebrospinal fluid); and (4) empyemas (bacteria grown from pleural fluid). Excluded from consideration within these categories were cultures positive for diphtheroids, Bacillus subtilis, staphylococci other than Staphylococcus aureus or Staphylococcus albus, and unidentified aerobic gram-negative bacilli which were either chromogenic or failed to give biochemical reactions characteristic of the common varieties of coliform organisms. Tubercle bacilli were also arbitrarily excluded from consideration.

The results of all bacteriological cultures made during the years of the survey were reviewed in detail and those from which significant organisms were grown from blood, cerebrospinal fluid, or pleural fluid were selected. The hospital records of the patients from whom these cultures were made during life were obtained and examined. For the purposes of the present analyses, only the age of the patient and the final result (that is, whether the patient died or recovered before leaving the hospital) were used. Parallel studies in patients in whom all such cultures were negative were not attempted because it was felt that the data derived could not be readily interpreted. As to the autopsies, the only aspects mentioned in this report are the finding of Staph. aureus in the postmortem cultures and whether or not this staphylococcus was demonstrated as the only or predominant organism in the cultures from some significant site.

Background Information

The background data from which this material was selected are given in figures 1 and 2. During the period of this study, the total number of admissions to the hospital rose above 43,000 in 1941 and then fell off to 33,600 in 1957, a drop of over 20%. During the same interval, the number of cultures processed in the bacteriological laboratory increased almost fivefold, from about 10,000 in 1935 to nearly 50,000 in 1957. Hereafter, the data will refer to the numbers of patients and not to the numbers of positive cultures.

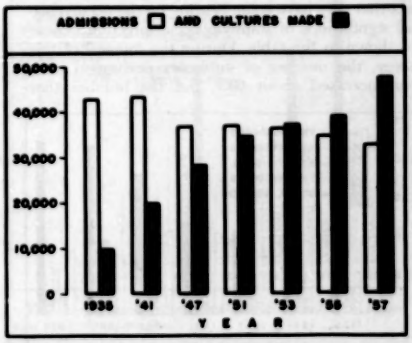

Fig. 2.—Admissions and cultures made in selected years at Boston City Hospital.

The total number of deaths each year from all causes is shown in the table. This number fluctuated somewhat but had a general downward trend, almost paralleling that of the total number of admissions, with about 17% fewer deaths in 1957 than in 1935. The number of deaths from all causes per 100 admissions to the hospital fluctuated somewhat throughout this period but generally was about seven.

The number of autopsies performed at the hospital (fig. 1) increased from about 700 to over 1,100, and those in which bacteriological cultures were made increased more than proportionally. The autopsy percentage for the entire hospital, that is, the proportion of fatal cases in which autopsies were performed, increased during the interval of this study from about 25% to nearly 50% (see table).

Staphylococci in Postmortem Cultures

Cultures made at autopsy are often difficult to interpret without much more detailed study than was made in the present survey. Therefore, it is possible to present, at this time, only certain crude data that may have some bearing on the occurrence and significance of staphylococcic infections; these are shown in the table. During the interval of this survey, the number of autopsies performed each year increased about 60%, but the number that yielded Staph. aureus increased to a much greater extent. The number of autopsies that yielded this organism in pure culture or as the only or predominant organism from one or more important sites (as far as could be determined from the bacteriological reports) likewise increased far out of proportion to the increase in the number of autopsies in which cultures were made. This may be taken as a very crude index of the increasing significance of Staph. aureus as a major or contributing cause of death.

Autopsies Performed and Occurrence of Staphylococcus Aureus in Postmortem Cultures in Each Year of Survey

Year	Admissions, No.	Deaths, No.	Deaths, %	Autopsies Performed	Deaths, %	Autopsies Cultured	Autopsies Yielding Staph. Aureus: Total, No.	Total, %*	Pure or Predominant, No.	Pure or Predominant, %*
1935	39,274	2,749	7.0	704	25.6	435	126	28.9	32	7.4
1941	43,170	2,669	6.2	869	32.2	685	268	39.2	101	14.7
1947	38,668	2,984	7.6	984	32.2	585	215	40.2	86	16.1
1951	39,412	2,680	6.8	913	33.8	705	325	41.0	193	24.3
1953	37,557	2,617	7.0	984	35.6	856	339	39.6	142	16.9
1955	34,769	2,512	7.2	1,089	41.3	914	410	44.8	204	22.2
1957	33,894	2,276	6.8	1,113	48.9	904	421	47.7	223	24.7

* = % of autopsies cultured.

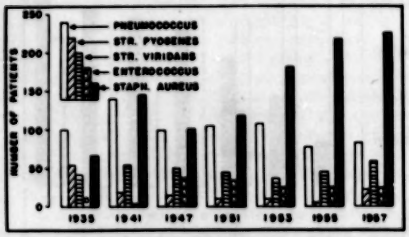

Fig. 3.—Bacteremia—occurrence of gram-positive cocci in blood cultures.

Occurrence of Bacteremia

The most significant trends were revealed by the cases of bacteremia. The numbers of patients with blood cultures positive for the most common gram-positive coccal organisms (other than Staph. albus, which will be considered separately later in this paper) are indicated in figure 3, and those whose blood cultures yielded the most common of the various important gram-negative bacteria are shown in figure 4. Pneumococcus was the most frequent invader of the blood stream in 1935; since then the number of patients with pneumococcic bacteremia has fluctuated slightly and showed a significant drop only in 1955 and 1957. Cases of hemolytic streptococcic (Streptococcus pyogenes) bacteremia were about half as frequent as those with pneumococcus in 1935, but their number declined sharply in the sulfonamide era. Very few such cases have been encountered since then and until 1957, when a moderate number again occurred. The numbers of patients with bacteremia due to streptococci of the viridans group fluctuated slightly and irregularly. On the other hand, enterococcic bacteremias were almost unknown or unrecognized before the

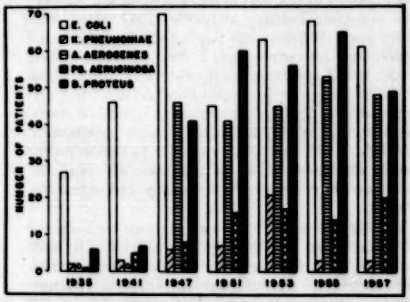

Fig. 4.—Bacteremia—occurrence of gram-negative bacilli in blood cultures.

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antibiotic era, but there have been 23 to 36 cases each year since then. The greatest and most significant increase occurred in the number of patients with bacteremia due to Staph. aureus. There was a sharp increase in 1941, a temporary decline after the early use of penicillin, and a steady increase

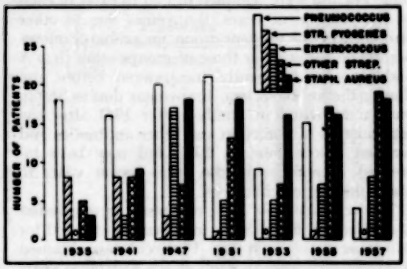

Fig. 5.—Meningitis—occurrence of gram-positive cocci in cerebrospinal fluid.

thereafter. In 1957 there were nearly four times as many cases as in 1935 and more than twice as many as in 1947.

The occurrence of invasion of the blood stream with various gram-negative bacilli showed an even more striking trend. These bacteremias were infrequently observed prior to the sulfonamide era, cases of Esch. coli bacteremia accounting for the great majority of those seen in 1935. Patients with Esch. coli bacteremia increased in number markedly after the introduction of the antibacterial drugs. Large numbers of cases have continued to occur since then, except for a temporary and partial remission after 1947, that is, after the broad-spectrum antibiotics came into use. Klebsiella pneumoniae (Friedlander's bacillus) bacteremia occurred in a small number of patients each year, with a moderately increased number in 1953. Aerobacter aerogenes had not been identified in blood cultures at all until after 1941; however, in 1947, bacteremia with this organism occurred in 46 patients, and there have been about that number of cases each year since then. Pseudomonas bacteremia was rare in 1935, but there has been a moderate and steadily increasing number of cases each year since then (up to 20 in 1957). There were six and seven patients with Proteus bacteremia in 1935 and 1941, respectively, and the number rose sharply during the antibiotic era until there were 65 cases in 1955 and somewhat fewer in 1957. Proteus organisms thus vie with Esch. coli for top place among the gram-negative bacteremias. Not shown in the figure are the cases of bacteremia due to Hemophilus influenzae and various species of Salmonella, including S. typhosa. These accounted for a small and fluctuating number of cases each year.

Occurrence of Bacterial Meningitides

The numbers of cases of meningitis due to the most common pathogenic bacteria are shown in figures 5 and 6. The pneumococcus (fig. 5) caused the largest number of cases through 1951, with irregular fluctuations in the numbers occurring subsequently and a sharp drop only in 1957. Some of these fluctuations are undoubtedly the result of the varying numbers of cases in which a definite diagnosis of the disease was established (cases of purulent meningitis with pneumococcic bacteremia) but are not included because cultures of the cerebrospinal fluid were sterile due to the administration of highly active antibiotics prior to the initial lumbar puncture. Thus, the drop in the number of cases of pneumococcic meningitis in 1957 is more apparent than real. A review of the records of patients with pneumococcic bacteremia during that year uncovered more than 20 patients in whom blood cultures were positive for pneumococci at the time of admission and who had signs of meningeal irritation with evidence of reaction in the cerebrospinal fluid. However, the first lumbar puncture in these cases was done after effective antibiotics had already been administered and both the blood culture and cerebrospinal fluid at that time yielded no growth. There were other such cases, but fewer in number, in each year after 1935.

Hemolytic streptococcic meningitis was second in frequency in 1935. The number of cases declined sharply after the introduction and widespread use of penicillin, and it has only rarely been encountered after 1947. Enterococci were not grown from

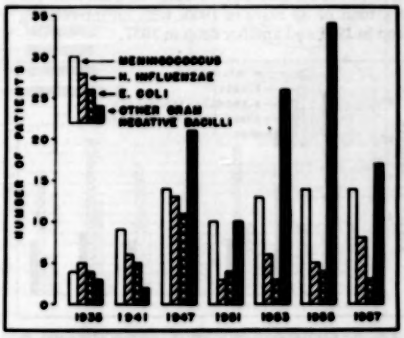

Fig. 6.—Meningitis—occurrence of gram-negative organisms in cerebrospinal fluid.

the cerebrospinal fluid of patients with meningitis in 1935; they were first recognized during the sulfonamide era and have since increased to about the extent to which the cases of hemolytic streptococcic infections have decreased. Other streptococci, namely those of the viridans group and of specific

groups other than A and D, showed a marked and irregular increase during the period of this survey and, taken together, were the most frequent gram-positive coccal organisms encountered in meningitis in 1955 and 1957. Meningitis due to Staph. aureus

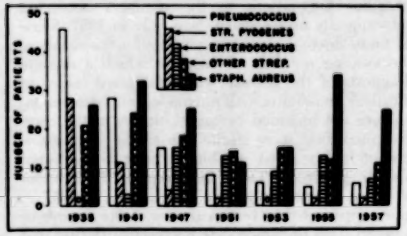

Fig. 7.—Empyema—occurrence of gram-positive cocci in pleural fluid.

likewise increased from 3 cases in 1935 to 18 cases in 1947, and there have been about that many cases in each of the subsequent years of this study.

Among the cases of meningitis due to gram-negative organisms (fig. 6), the numbers of those caused by meningococcus or H. influenzae fluctuated irregularly during the years of the survey. Cases of Esch. coli meningitis apparently increased through 1947, then declined sharply, and have been infrequent since then. On the other hand, cases of meningitis due to other gram-negative bacilli, which include mostly Aerobacter, Proteus, and Pseudomonas organisms, were infrequent at first; these increased markedly during the antibiotic era to a total of 33 cases in 1955, with an intervening drop in 1951 and another drop in 1957.

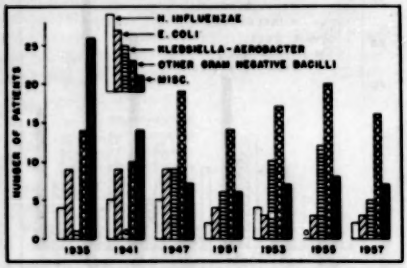

Fig. 8.—Empyema—occurrence of various organisms in pleural fluid.

Occurrence of Empyema

In the cases of empyema (fig. 7 and 8), as in the meningitides, the pneumococcus was the most frequently found organism, and hemolytic streptococcus was second in frequency in 1935. The number of pneumococcic empyemas (fig. 7) declined sharply and steadily from 46 cases in that year to only 5 or 6 in each of the last three years that were surveyed. Meanwhile, the numbers of hemolytic streptococcic empyemas dropped to or near the vanishing point after penicillin and the other antibiotics achieved wide use. Here, too, enterococci were first encountered in empyemas after the sulfonamide era and were obtained in 7 to 15 cases in each of the subsequent years. Empyemas due to other streptococci (the viridans group, anaerobic or microaerophilic varieties, or those of groups other than A and D) were frequently encountered before and during the antibiotic era. Empyemas due to Staph. aureus decreased in number after 1941 after the introduction of penicillin and other antibiotics and reached a low point in 1951, but they have increased in number in the more recent years to about the prepenicillin level.

The occurrence of other organisms in empyemas is depicted in figure 8. H. influenzae accounted for five cases or less each year. Esch. coli was obtained from eight patients in each of the first three years that were surveyed and from only three or four patients in each of the later periods. Organisms of the Klebsiella-Aerobacter group were rare in empy-

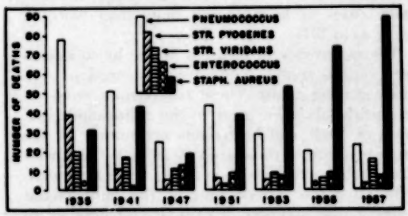

Fig. 9.—Bacteremia—deaths in patients with gram-positive cocci in blood cultures.

emas before 1947 when there were 9 cases; since then there have been 3 to 13 cases each year, only 1 to 3 of them due to Friedlander's bacillus. Other gram-negative bacilli, Proteus, Pseudomonas, Bacteroides, or unidentified species, have accounted for 10 to 20 empyemas each year, with irregular fluctuations. Other organisms, chiefly clostridia, fusiform bacilli, and spirilla, were the most frequently found bacteria in 1935 and caused 27 cases of empyema. This number declined steadily to less than one-third of that number by 1947 and has remained at about that level since then.

Deaths in Patients with Bacteremia

Most revealing were the trends in the actual number of deaths among patients with blood cultures positive for various bacteria (fig. 9 and 10). Pneumococcus and hemolytic streptococcus (fig. 9) caused the largest number of deaths in 1935 (78 and 39 respectively). The number of deaths in patients with pneumococcic bacteremia declined markedly with the successive introduction of the sulfonamides and antibiotics; fatal hemolytic strep-

tococcic bacteremias declined sharply after 1935, and there have been very few deaths in such cases or none at all in the years surveyed during the antibiotic era. Deaths in patients with Streptococcus viridans bacteremia decreased steadily to 1951

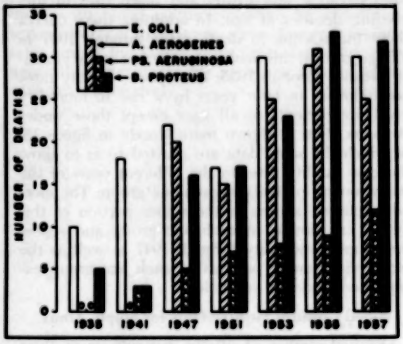

Fig. 10.—Bacteremia—deaths in patients with gram-negative bacilli in blood cultures.

but were again occurring in moderate numbers in 1957. There were no fatal cases of enterococcic bacteremia in 1935, but these accounted for 5 to 13 deaths each year from 1947 on. The number of deaths in patients with Staph. aureus bacteremia decreased markedly after 1941 when penicillin came into wide use, but the numbers of such deaths have increased nearly fivefold between 1947 and 1957.

Deaths among patients with gram-negative bacillemias (fig. 10) showed equally striking trends. Except for a slight remission in 1951, after the introduction of the broad-spectrum antibiotics, the number of fatal cases of Esch. coli bacteremia increased steadily from 10 in 1935 to 30 in 1953, and there have been about the same number in each of the later years. A. aerogenes was first encountered in the blood of fatal cases during the antibiotic era; since 1947, however, the number of deaths in patients with Aerobacter bacteremia have closely approximated those in which Esch. coli was the invader of the blood stream. The number of fatal cases of Pseudomonas bacteremia increased steadily from none in 1935 to 13 in 1957. Highly significant was the increasing number of deaths among patients with Proteus bacteremia which increased from 3 to 5 in each of the preantibiotic years to more than 30 deaths in 1955 and 1957.

Summary of Occurrence and Mortality

Patients with Bacteremia.—The total numbers of patients and deaths for each year of the study are summarized for all the bacteremias in figure 11. Patients in whom Staph. albus was the only organism grown in the blood cultures are also indicated separately in this figure; however, those whose blood yielded only other organisms that were considered to be contaminants, notably diphtheroids, B. subtilis, and unidentified gram-negative bacilli, were excluded entirely. From the lower portion of figure 11, it is seen that the total numbers of patients whose blood cultures yielded significant pathogens increased more or less steadily over the entire period of the study, whereas those with blood cultures positive only for Staph. albus fluctuated only slightly after 1941. The total number of deaths in each of the successive years of the survey (shown in the upper left portion of figure 11) declined only slightly from 1935 through 1947, but the number of deaths has been increasing steadily since then and has rapidly surpassed the number that occurred in 1935. By 1957 there were nearly 50% more deaths among patients with bacteremia than there had been in 1935.

The case fatality rates for the different years of the study for all patients with bacteremia and for those in which Staph. albus was the only organism in blood cultures are shown in the upper right panel of figure 11. The greatest drop in death rates in the bacteremia cases, irrespective of whether or not those yielding only Staph. albus are included, occurred during the sulfonamide era; only a relatively small further decline occurred between 1935 and 1941. Since 1947, however, the case fatality rates have been climbing slowly but steadily, although they are still far below the 1935 level.

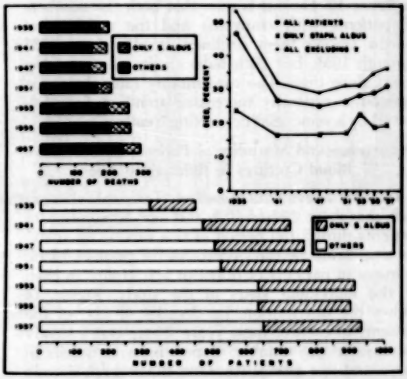

Fig. 11.—Patients with positive blood cultures—occurrence and mortality.

The case fatality rates in the cases having only Staph. albus was much lower than in the others and showed only minor fluctuations.

Patients with Meningitis.—The over-all picture for the patients with bacterial meningitis is shown in figure 12. As shown in the lower portion of the figure, the total number of patients with all forms

of bacterial meningitis fluctuated throughout the study, with a generally increasing trend. The number of deaths also fluctuated, but with a generally decreasing trend, as depicted in the left upper part of the figure. The case fatality rates for all cases of

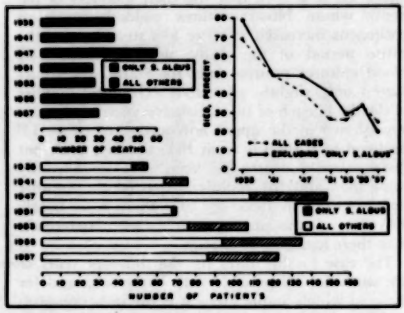

Fig. 12.—Bacterial meningitis—occurrence and mortality.

meningitis are summarized in the upper right panel of figure 12. There was a marked and more or less steady fall in these rates over the entire period of the study for all of the cases, whether or not those yielding only Staph. albus are included.

Patients with Empyema.—A similar representation of the data for all of the empyemas is offered in figure 13. Here it is seen that both the numbers of patients with empyema and the numbers of deaths among them declined steadily from 1935 through 1951, but both have shown an increasing trend since then. The case fatality rates, however, showed a generally increasing trend at first, followed by a somewhat decreasing trend.

Occurrence and Mortality of Patients with Positive Blood Cultures in Relation to Age

In order to evaluate the effect of possible changes that may have occurred in the age distribution of patients during the period of this survey, an analysis was made of the occurrence of positive blood cultures in patients of different age groups in each of the individual years of the study. Figure 14 shows the distribution, by decades of age, of the patients in each of these years. There was a steady increase in the number of patients and deaths in the oldest age groups (those of the seventh decade or older). The number of infants and children under 10 years of age who had positive blood cultures fluctuated at first and then increased sharply after 1953. This latter rise is a reflection of the more thorough study that such patients have been receiving after reorganization of the pediatric service of the Boston City Hospital, which, at that time, became a university-affiliated service with a full-time senior staff.

The case fatality rates in the successive age groups, as shown in the curves depicted in the upper portion of figure 14, are all very similar for the different years. They show a drop in mortality after the first decade of life, low rates in the second and third decades, and steady and sharp rises in succeeding decades of age. In addition, these curves show the decline in death rates through 1947 in all age groups, this decline continuing in the younger decades through 1955; these lower fatality rates are followed in later years by a rise in mortality involving patients of all ages except those under 10 years. This is shown more clearly in figure 15, in which the same data are charted so as to show the case fatality rates in the different years of the study among patients of each age group. The mortality curves, shown in the upper portion of this figure, are similar in each age group and reflect the drop in mortality through 1947 as well as the recent rise among patients of each age group except those under 10 years old.

Blood Cultures Positive Only for Staph. Albus

Detailed studies of all the patients or of their hospital records were not included in this survey. The true significance of the occurrence of various organisms, particularly in routine blood cultures, cannot therefore be attested for all of the patients. In many instances careful study of the records, or

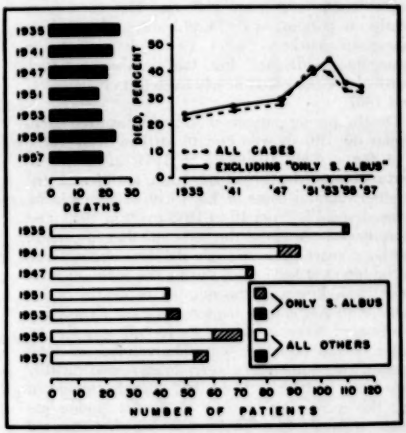

Fig. 13.—Empyema—occurrence and mortality.

even personal observations of the patients, have failed to provide conclusive evidence of the pathogenic role of the particular organism that was cultured. This is especially true of Staph. albus and, perhaps to a somewhat lesser extent, of some of the coliform organisms. The data in figures 14 and

15 excluded patients whose blood cultures yielded only Staph. albus; similar analyses of the numbers of the latter patients and of the deaths among them are shown in figure 16. Similar relationships were observed in patients whose blood cultures yielded only Staph. albus as were observed among those with blood cultures positive for significant organisms other than Staph. albus. The case fatality rates among the Staph. albus cases, however, were generally much lower for each age group and in each year of the study.

Some of the numbers of cases may reflect, to some extent, the susceptibility of various organisms to modern chemotherapy and be somewhat distorted as a result. Thus, the number of patients with bacteremia, meningitis, or empyema after 1935 may be lower than the actual number of such patients observed among those with highly susceptible organisms, such as pneumococcus or hemolytic streptococcus. The difference would consist of patients who may have received effective therapy before the materials for the cultures were obtained. The possible distortion in the number of patients with pneumococcic meningitis in 1957, as already noted, is an example in point. There were also several patients with empyema complicating pneumococcic pneumonia whose initial thoracentesis yielded purulent pleural fluid that gave no growth. In some of these fluids, pneumococci could still be identified in direct smears, but these patients were excluded from the present study because the cultures of the same and subsequent fluids yielded no growth. In as much as such cases generally had a favorable outcome, the results

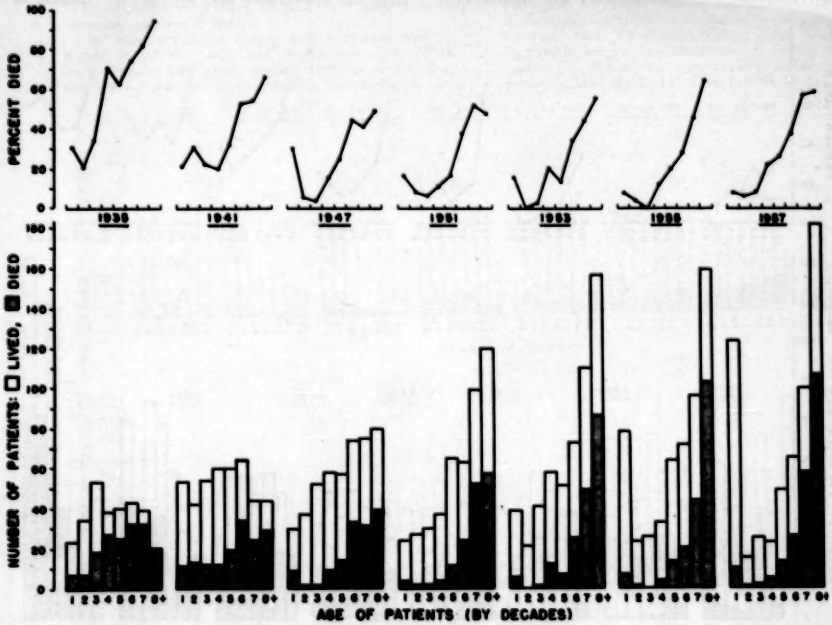

Fig. 14.—Occurrence of positive blood cultures and outcome in different years according to age of patients (excluding those with only Staph. albus).

Comment

It has been possible in this paper to present only the bare facts; the possible interpretations and implications will not be discussed here. We have been dealing only with hospitalized patients among whom antibacterial agents were used intensively. We believe that these findings are, for the most part, real, as exemplified by the fact that all age groups were involved both in the drop in mortality in bacteremic patients after introduction of the antibacterial drugs and in the subsequent tendency for the mortality to rise.

among the groups of cases with susceptible organisms were probably even better, as far as mortality is concerned, than those depicted in the figures.

The favorable impact of the antibacterial drugs, at least as revealed in the data from this one hospital, has been accompanied by variable changes in the numbers of patients and has been reflected primarily in a marked reduction in the number of deaths from serious infections due to certain common bacterial pathogens, notably pneumococcus and hemolytic streptococcus. This, however, has been generally overshadowed by the greater increase in the number of cases and deaths from other serious infections and blood stream invasions with Staph. aureus and with certain other organisms, notably enterococci and the coliforms, including Aerobacter, Proteus, and Pseudomonas organisms. These had not previously been considered highly pathogenic and had only infrequently caused fatal infections before the era of antibacterial drugs. The net result has been a drop in the number of deaths from bacterial infections through 1947, followed by a significant and steady increase beyond that which antedated the era of antibacterial drugs.

In over-all effectiveness, as reflected in case fatality rates in serious infections, the most favorable effect of the antibacterial agents would seem to have been exerted during the sulfonamide era, with only a slight further improvement during the period when the use of penicillin and streptomycin was becoming very popular. This was followed by a steady increase in the total number of cases and deaths from bacterial infections and reduced effectiveness of the drugs against staphylococcus infections. These infections increased in incidence, along with the appearance and increase in numbers of cases of infections with enterococci and coliform organisms, against which the available drugs have only relatively slight activity.

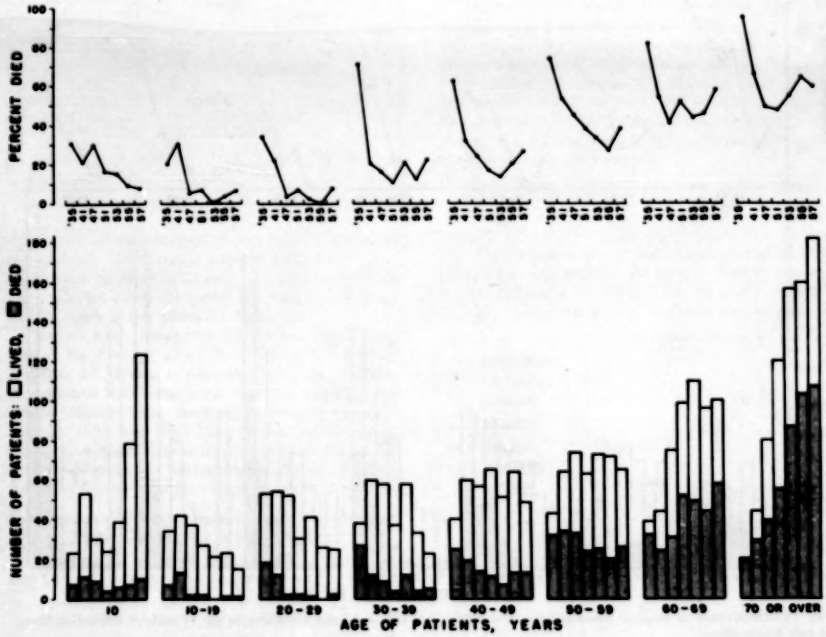

Fig. 15.—Number and outcome of patients of various ages having positive blood cultures in the years surveyed (excluding those with only Staph. albus).

Conclusions

These findings could be interpreted as pointing to the immediate need for broadening the scope of the current search for new antimicrobial agents to include not only the resistant staphylococci but also the relatively resistant coliform organisms. However, it would appear to be more pertinent to direct research toward evaluating in detail and attempting to overcome the profound changes pro-

duced by the antibiotics in the host and in his total bacterial flora, changes which seem to enhance the number, pathogenicity, and invasiveness of various micro-organisms which, under ordinary circumstances, appear to be rather benign. Even more, the findings presented here point to the urgent need for methods of broadly increasing resistance against bacterial infections in general, and particularly against those in which currently available antimicrobial agents do not appear to be highly effective.

These studies were aided, in part, by a grant from the National Institutes of Health.

The authors wish to express their appreciation to the Misses Marion E. Lamb and A. Kathleen Daly of the Bacteriological Laboratory, Mallory Institute of Pathology, who carried out and made available bacteriological data.

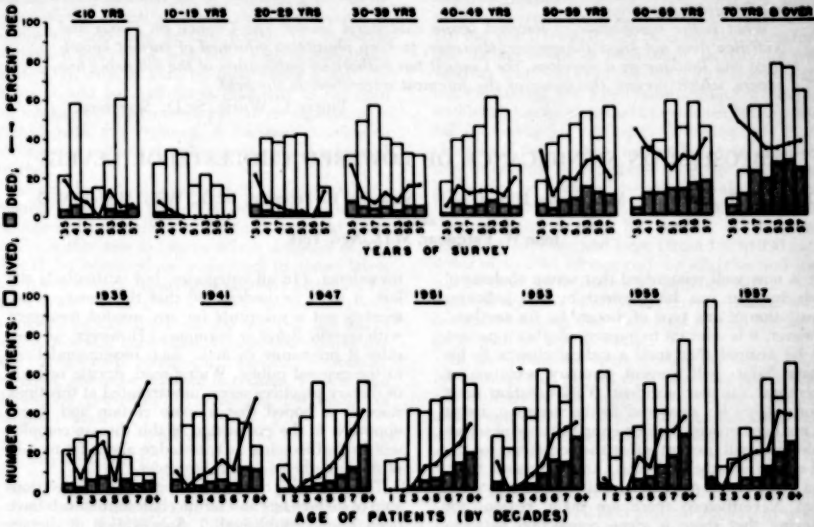

Fig. 16.—Occurrence and outcome of patients with blood cultures positive only for Staph. albus.

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COUNCIL ON FOODS AND NUTRITION

Many factors are now known to affect the concentrations of various lipids in the serum. Diet, although important, is but one factor. The significance of induced variations in serum lipids to atherogenesis is not clear, but cholesterol levels and methods of manipulating them have become of utmost interest. The likelihood of harm arising from these fluctuations seems remote, although we must hasten to add that final proof of harmlessness is not available.

The physician who is confronted with the immediate problem of a patient who has survived a coronary attack or with a patient who has an elevated serum cholesterol value and whose familial history shows a tendency toward fatal heart conditions is searching for guidance toward rational treatment. Because the answer is not at hand, confusion has resulted. Pressure from the patients and their families, pressure from the promoters of certain drugs, and his own determination to apply the most beneficial measures to these patients have left the physician in a frustrating position.

What is the significance of lowered serum cholesterol levels? The Council on Foods and Nutrition does not know the answer. However, to keep physicians informed of current knowledge and thinking as it develops, the Council has authorized publication of the following five papers, which present the views of the foremost researchers in the field.

PHILIP L. WHITE, SC.D., *Secretary.*

SYMPOSIUM ON SIGNIFICANCE OF LOWERED CHOLESTEROL LEVELS

Edward H. Ahrens Jr., M.D., Jules Hirsch, M.D., Malcolm L. Peterson, M.D., Willy Stoffel, M.D.
and
John W. Farquhar, M.D., New York

It is now well recognized that serum cholesterol levels in man can be lowered by the judicious substitution of one type of dietary fat for another.[1] However, it is relevant to inquire whether a patient can be assured that such a radical change in his dietary habits will prevent coronary occlusion or a cerebral vascular accident. This question must unfortunately be answered in the negative, for it has not been proved that lowering the level of serum cholesterol will prevent either the occurrence or the end-results of atherosclerosis. At the present time, clear proof of this proposition still seems many years away. Nevertheless, there are many reasons for believing that there is some connection between cholesterol metabolism and atherosclerosis, and, while waiting for elucidation of this relationship by laboratory workers, it seems justifiable to apply certain dietary procedures that are theoretically harmless and possibly beneficial.

We have stated previously[2] that such measures can be recommended to patients with manifestations or complications of atherosclerosis, i. e., to patients who have angina pectoris or peripheral vascular disease, to those who have had coronary occlusion or a cerebral vascular accident, to those with a strong family history of such illnesses, to patients with hypercholesteremia and/or xanthomatosis of tendons or skin, and finally to patients with diabetes or myxedema. (In all categories, but particularly the last, it must be understood that the dietary treatment is not a substitute for any needed treatment with specific drugs or hormones.) However, we consider it premature to make such recommendations to the general public. Widespread, drastic revision of dietary practices seems unwarranted at this time, since it is hoped that a more certain and direct approach to the prevention of this disease complex will be forthcoming as knowledge about fat metabolism and atherosclerosis advances.

The following conclusions regarding the relationship of dietary fats and serum cholesterol levels have been firmly established. 1. Substitution of dietary fats rich in polyunsaturated fatty acids for those rich in saturated acids will lower cholesterol levels in almost every person, whether normocholesteremic or hypercholesteremic.[3] 2. The greater the substitution, the greater the effect; thus, little benefit is obtained by merely adding a supplement of polyunsaturated fat to an otherwise unchanged diet. For the maximum dietary effect at least 75% of the calories derived from fat must be of the polyunsaturated type, and the proportion of calories from fat in the total caloric intake must be 40% or higher. 3. The effects described are due to differences in fatty acid structure and not to trace factors in dietary fats such as vitamins, minerals, sterols, or other undefined nonfatty acid substances. 4. The effects

From The Rockefeller Institute.

described are not caused by "essential fatty acids," but more likely by a wide array of polyunsaturated acids.[4] Furthermore, there is no evidence to support the contention that human atherosclerosis is a manifestation of essential fatty acid deficiency. 5. The oral administration of other agents (such as sitosterol or nicotinic acid) also decreases serum cholesterol levels, but presumably by other mechanisms.

These findings can be translated into practical terms as follows: (1) strict avoidance of all meats, egg, and dairy products, except as rare treats; (2) minimal intake of partially hydrogenated fats such as in spreads and mayonnaise, regardless of the source of the fat which is hydrogenated; (3) substitution of fish or seafood for meat (preferably twice daily), with occasional use of fowl and generous intakes of egg white, skimmed milk, and gelatin to assure an adequate protein intake; (4) ingestion with each meal of at least one ounce of polyunsaturated fat, such as corn oil three times a day. Patients should be acclimated gradually to the corn oil intake over a two-week period. As experience is gained with this regimen, it becomes possible to incorporate some of the oil in cooking and in special recipes.

Serum cholesterol levels should be followed by a reliable laboratory test every two to three months to assure that an effect is obtained and held. Generally, within one to two months a decrease of 30% should be obtained as compared to those levels measured during ingestion of ordinary saturated fat diets. Few patients with hypercholesteremia will achieve "normal" levels of 200 mg. per 100 ml. of serum, but skin xanthomas usually decrease in size and occasionally disappear. Tendon xanthomas, however, are more resistant to change. Weight gain should be prevented by reducing the intake of carbohydrates.

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Since the plasma cholesterol level is elevated in myxedema, diabetes, nephrosis, and obstructive jaundice, falling levels observed in treatment of these conditions give additional proof that the disease is abating or responding to therapy. However, in obstructive jaundice, a fall in level of cholesterol without a fall in serum bilirubin level may be an ominous warning of parenchymal liver damage. In familial xanthomatosis also, falling levels of plasma cholesterol are evidences of response to diet, drugs, or heparin and may foretell resorption of yellow plaques in the skin.

The normal level of plasma cholesterol, in adults or children living on a diet of vegetables and fish, is between 120 and 160 mg. per 100 ml. Levels under 120 mg. per 100 ml. are usually due to diseases of the liver or the jejunum. However, very few people can approach this optimal level when the diet contains eggs, dairy products, and animal fat. Experience has shown that in animals, chickens, and men atherosclerosis is minimal or absent, and intravascular thrombosis is very rare, when the diet is such as to maintain blood cholesterol levels under 180 mg. per 100 ml. It may be concluded, therefore, that falling levels of cholesterol, in patients with vascular accidents or in persons with levels over 200 mg. per 100 ml. and a bad family history of vascular accidents, can be regarded as evidence of a successful prophylactic regimen. Lowering of blood cholesterol level, even in familial xanthomatosis, may be effected by vegetarian diets, but much lower levels can be achieved by administration of nicotinic acid and regulation of diet. Daily administration of heparin may be needed in the most refractory subjects, and large (from 180 to 300 mg.) doses of thyroid extract may be effective and well tolerated in some euthyroid patients. All of these methods are more effective in coronary disease without xanthomatosis, but the use of thyroid extract in these patients seems unwise.

In some families, high levels (300 mg. per 100 ml. or more) of plasma cholesterol are noted, with no tendency of the members to coronary disease, and occasionally, in those with familial normotensive levels in the senium, with notable longevity. Also, many men have lived on a normal diet for decades after coronary disease became manifest. In the culture found in the United States, coronary atherosclerosis develops rapidly in adolescent white males and in Negro boys and girls alike. The studies of Lober[1] showed that the average man of 30 years of age, in Minneapolis, has 60% as much coronary lipid intimal infiltration as is found in men dying of coronary occlusion. Later in life, thrombotic accident rather than xanthomatous occlusion becomes the common feature of the disease. Yet even in older persons, a lowered blood cholesterol level may be evidence of the success of a dietary regimen that will retard thrombosis and accelerate thrombolysis. Unfortunately, even in a dependable laboratory, routine measurements of cholesterol vary between 20 to 30% in a given subject on a constant regimen, when such measurements are followed for months. In a few laboratories, values may vary by 100% in the same plasma submitted on different days.

From the College of Medicine, State University of New York.

Studies of thrombophilic tendency and of fibrinolysis are even more exacting and rarely dependable, except in research laboratories. Thus, the physician may well feel that the cost of undependable tests outweighs their value and that duplicates are needed to establish an abnormal level or a lowering in response to management. He may prefer to use dietary control and the largest tolerated daily intake of nicotinic acid to reduce cholesterol and the thrombotic tendency in patients who have high risk and a desire to reduce this risk as much as possible at reasonable inconvenience and expense.

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W. Stanley Hartroft, M.D., Ph.D., St. Louis

To the pathologist, the significance that lowered levels of serum cholesterol might have in the prevention or amelioration of atherosclerosis in man hinges on the question, "How fundamental is the role of this substance in atherogenesis?" Cholesterol, in both free and esterified forms, is present in higher quantities in atheromatous arteries than in normal ones. This fact, recognized by pathologists for more than a century, has been verified repeatedly by direct biochemical estimations of lipids in the tissue. Pertinent data of this type have been obtained from coronary arteries of patients dying of myocardial infarction in which four times as much cholesterol was found as in those of patients dying of other causes.[1] The cholesterol, phospholipid, and neutral fat ratios in arterial walls, however, are the same as those of blood plasma,[2] raising the question, "Why should cholesterol in the serum be given more pathogenic emphasis in atheroma than the other lipids?" One of the strongest arguments, of course, for emphasizing cholesterol in this connection stems from Anitschkow's [3] demonstration in 1913 that cholesterol-containing foods are atherogenic for the rabbit. This discovery initiated a series of experiments that swept the laboratories of the world and has absorbed the attention of medical scientists ever since.

More than a century ago, Rokitansky proposed the thrombogenic view of atheroma, namely, that the lesions may be the result of organization of mural thrombi clinging to arterial walls. Recently, experimental evidence to support this view has been obtained by a number of investigators.[4] After having been eclipsed for the past half-century by the discovery of Anitschkow, the thrombogenic theory of atherogenesis is enjoying a rebirth and new vogue. Its renaissance has been fostered by reports that certain fats, which have the ability to elevate cholesterol levels in the blood, decrease silicon-treated tube clotting time [5] and prolong the time required for lysis of clots by streptokinase.[6] These observations suggest that lowered levels of serum cholesterol may have at least an indirect significance in atherogenesis, even from the viewpoint of the Rokitansky hypothesis.

The laboratory of Washington University conducted experiments on the production of renal and myocardial infarction in rats by dietary means alone.[7] Levels of serum cholesterol in rats that developed infarcts were not significantly higher than those in animals fed the same diets and that did not develop infarcts. As is the case with most studies in man, although a rough correlation between infarction and high levels of serum cholesterol was present for group studies, the development of an infarct in an individual rat could not be predicted on the basis of its level of serum cholesterol.

These and other findings recently have influenced my colleagues and me to direct our attention to other abnormalities of lipid metabolism. A pathological lipid can be demonstrated histochemically in variable amounts, frequently in abundant quantities, in atheromatous lesions of man.[8] This substance is the pigment ceroid, formed by auto-oxidation or peroxidation of unsaturated fats.[9] Although often intensely sudanophilic, it is not extracted by fat solvents, being left behind in the "nonfat" residue when lipids of arterial walls or plaques are analyzed biochemically. Atheroma is a pathological lesion, and perhaps it is not unreasonable that a pathological lipid (such as ceroid) should be sought to elucidate atherogenic mechanisms. Lately, we have encountered ceroid in a number of recently formed thrombi of coronary arteries obtained at autopsy from patients with fatal cases of myocardial infarction. In our dietary experiments, we have previously reported [7a] the presence of this abnormal lipid in mural thrombi in the hearts of rats in which myocardial infarcts developed.

The question of the importance of lowered levels of serum cholesterol in man in relation to atherogenesis and coronary heart disease must receive continued attention and study by investigators of this disabling and frequently fatal condition of man. Considerable evidence, however, some of which has been cited, indicates that variations in the level of this substance in circulating blood may be related only indirectly in a *pari passu* fashion to atheroma and its complications. Pathological studies, in both man and animals, in this laboratory and others, have suggested to us that, when all the facts are finally uncovered, it is not unlikely that some other substance or substances in plasma may have a more direct bearing on the problem of atheroma than does cholesterol. This view by no means implies that continued investigation of cholesterol metabolism should not be pursued intensively because, through these efforts, the key to what is undoubtedly a highly complex problem may be

From the Department of Pathology, Washington University Medical School.

uncovered—hopefully, in the near future. In the interim, there is probably little reason to recommend attempts to lower cholesterol levels in the serums of healthy men and women as long as those values fall within the usual ranges for people in the United States. For those persons who have had a heart attack, the decision to institute procedures to lower their levels must still depend (as with other therapeutic procedures for any major disease) on the acumen and judgment of the informed individual physician.

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By and large, one speaks with authority about those things which he is able to measure. Unfortunately, the ability to measure and the ability to understand do not necessarily go hand in hand. Of all the chemical compounds that are measured in clinical laboratories, there is none about which more has been written and about which less is understood than cholesterol.

In the human subject, roughly two-thirds of the amount of cholesterol found in the plasma is esterified with fatty acids. It seems highly probable that, in one way or another, it is vitally implicated in the over-all transport mechanisms involved in fatty acid metabolism. One cannot go beyond this until further data have become available.

From a clinical standpoint, it is well established that, statistically, elevated levels of cholesterol are found in association with atherosclerosis. It seems reasonable to believe, therefore, that physiological measures directed toward lowering the level of the blood cholesterol and related lipids may work in a desirable direction from the standpoint of formation and progression of atherosclerotic lesions. Since cholesterol and related lipids are normal, essential parts of the basic economy of the organism, it is obvious that any attempt to "get rid of" these compounds would be both unphysiological and impossible. Therefore, the objective should be that of achieving normal cholesterol metabolism with consequently normal blood levels, in the hope that such a program will prevent abnormal deposition of lipids in the vessels and possibly mobilize existing atheromatous lesions. With the aforementioned objective in mind, a variety of programs have been proposed.

For many years, the elimination of cholesterol from the diet had a considerable vogue.[1] When it became apparent, however, that endogenous cholesterol formation was a much more important factor than exogenous intake, this dietary approach fell into deserved disrepute.

A second strong school of thought held the opinion that dietary fats in general elevated the level of plasma cholesterol and were "pro-atherosclerotic" in their effects.[2] On the basis of this type of concept, the low-fat diet had a strong list of proponents for some years and is still regarded favorably in some quarters.

Work begun eight years ago in the laboratory of the Institute for Metabolic Research and subsequently confirmed in many parts of the world has indicated that it is unsound to "lump" dietary fats, with respect to their effects on plasma cholesterol. Vegetable fats, rich in linoleic acid, lower plasma cholesterol, and animal fats, which contain predominantly saturated and monounsaturated fatty acids, have a significant elevating effect on plasma cholesterol.[3] On the basis of these observations, diets have been constructed in which a proper balance can be achieved between polyunsaturated fats and saturated fats.[3a]

At the 2,000-calorie level, such diets contain approximately 80 Gm. of protein, 170 to 200 Gm. of carbohydrate, and 100 to 115 Gm. of fat, including approximately 58 Gm. of linoleic acid. The following diets are now being used to achieve and maintain cholesterol levels at 180 mg. per 100 ml. or below and other lipids in a proportional range.

The group 1 diet contains no animal fat. Protein is supplied by nonfat milk, nuts, cereals, and vegetables. The group 2 diet differs from the group 1 diet by including fish, fowl, and liver, with a slight

From the Institute for Metabolic Research, Highland-Alameda County Hospital.

reduction in nonfat milk protein. The group 3 diet is the same as the group 2 diet, with the addition of 4 oz. of lean beef, veal, lamb, lean ham, or egg and a further reduction of nonfat milk protein. The usual procedure is to place an atherosclerotic patient first on the group 1 diet and then proceed to group 2 and group 3 diets as indicated by the changes in his plasma lipid level.

In some patients with advanced atherosclerosis, even the group 1 diet fails to bring the plasma cholesterol and other lipids to normal levels (below 200 mg. per 100 ml.). Such patients are given a "safflower-milk" diet, consisting of an emulsion of 300 Gm. of Saf-Lac powder (1,700 calories), with sufficient low-carbohydrate vegetables and fresh fruit to bring the total intake to 2,000 calories. (Saf-Lac is a modified milk preparation which is free of butterfat and contains 40% safflower oil. It is a dried powder which is readily reconstituted when water is added.) This diet provides approximately 85 to 90 Gm. of linoleic acid.

A variety of pharmacological agents have been used to lower cholesterol. Among these, only large amounts of nicotinic acid [4] and very large quantities of β-sitosterol appear to be at all effective.[5] (Recent reports on certain of the iodothyronines are also of interest in this connection.)

From all the foregoing, it would appear reasonable to say, in our present state of ignorance, that if one can choose between a regimen that will produce a normal level of plasma cholesterol and one that will produce an elevated level of plasma cholesterol, then the former is the regimen to be selected. In the vast majority of persons with elevated plasma cholesterol levels, a diet that contains an adequate amount of polyunsaturated fat, with appropriate reduction in saturated fat, will achieve such a result.

From the standpoint of prophylaxis, it seems appropriate to raise the question of whether a relative deficiency of polyunsaturated fat in the diet, with a proportional increase in saturated fat, may be one of the important factors responsible for the high incidence of atherosclerosis that afflicts the middle-aged and elderly population of the United States. The disease also is present in many young adults, on the basis of autopsy findings in soldiers killed in Korea.[6] If this concept is correct, attention to revision of the over-all American diet is very much in order. One of the logical measures that can be used in such an approach is the replacement of hydrogenated fat with natural polyunsaturated fat in such foods as shortening and margarine.

Saf-Lac is manufactured by the Carnation Company.

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Valuable but confusing information on serum cholesterol has been derived from epidemiologic dietary studies. The sharp fall in the death rate from circulatory disease in many European countries during World War II was associated with a decreased consumption of milk, butter, and eggs. However, this decrease in fat consumption was coincident in Norway with a decreased protein consumption, as well as a decreased incidence of schizophrenia and suicide. Moreover, in Britain, the death rate from ischemic heart disease began to rise in 1943, although rationing was stringent until 1946. Similar studies are difficult to evaluate. Elaborate epidemiologic surveys have been done in South Africa, Italy, Spain, Guatemala, and Japan, relating the incidence of ischemic heart disease to serum cholesterol level and diet. Generally, these studies suggest that the level of serum cholesterol and the level and nature of dietary fat have a bearing on the incidence of ischemic heart disease.

From the Veterans Administration Hospital.

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Although cholesterol may be related experimentally to atherosclerosis, the damage associated with atherosclerosis is frequently due to thrombotic arterial occlusion. In experimental animals, plaques can be formed, intima roughened, and spontaneous myocardial infarctions produced, but only with extreme dietary manipulations. Therefore, much interest in the role of fat in blood coagulation has been shown. Two abnormalities have been found: 1. A shortened clotting time of plasma with Russell's viper venom was found when fat was added from plasma or milk. 2. A small decrease in the silicon-treated tube clotting time of man was observed after a fatty meal. Since changes in clotting time have not yet been shown to be necessarily related to thrombosis, no conclusions are justified from these interesting observations.

To discuss the significance of lowered serum cholesterol level, one may assume either that atherosclerosis and hypercholesteremia are causally related or that an elevated serum cholesterol level empirically is "bad." If the serum cholesterol value returns to normal, is further atherosclerosis prevented? Can a patient whose level of serum cholesterol is lowered to normal absorb lipid arterial plaques and restore a smooth intimal endothelium? These are important questions to which answers are presently unknown.

In treating patients with an increased level of serum cholesterol, restriction of calories to achieve optimum body weight should be heartily recommended. Reduction in weight is sometimes accompanied by a reduction in serum cholesterol, particularly if the level of serum cholesterol is initially elevated, but the amount the serum cholesterol falls is not determined by the degree of initial obesity.[1] Exercise is encouraged within the tolerance of the patient. The studies of Mann and co-workers [2] have shown that, during periods of increased caloric intake, the serum cholesterol value remains more or less stable if one exercises sufficiently to prevent weight gain. However, when the same caloric intake is maintained and exercise is reduced, increased total body weight is accompanied by increased levels of serum cholesterol. These findings support the thesis that serum cholesterol level increases when more calories are consumed than are required to maintain normal weight. Morris and co-workers [3] have published some fascinating studies which show a strong association between the amount of physical work performed and the incidence and severity of coronary artery disease. They found that London postmen and bus conductors (who climb the double-decker buses) had lower early-mortality rates from myocardial infarction than did their co-workers who were bus drivers and telephonists. Furthermore, heavy workers tended to have a more benign form of coronary artery disease than did the light workers. Although serum cholesterol levels have not been reported on these subjects, a study of their uniform sizes revealed that the drivers were bigger than conductors, even when they started work at age 25 to 29 years.

If a patient's serum cholesterol value remains high after optimum weight is achieved, certain drugs or diets may be used in an attempt to lower the level to the normal range. Nicotinic acid in large doses (3 to 6 Gm. per day) has proved to be an effective drug. It does not lower the level of serum cholesterol in all patients, and some patients cannot tolerate this amount of nicotinic acid because of gastric irritation. Since its mechanism of action in lowering serum cholesterol level is not yet known, it is considered an experimental drug in the doses used at the present time.

Estrogenic preparations have been used to reduce the level of serum cholesterol. After three months of estrogen therapy in a group of 51 men with myocardial infarction, there was a fall in serum cholesterol level (borderline statistical significance) and an increase in serum phospholipid.[4] Serial testicular biopsies showed depression of cellular activity. In patients with extensive xanthoma, gradual disappearance of the lesions was noted. This is encouraging, but occurrence of gynecomastia, diminished libido, and impotence thus far has restricted the use of this therapeutic approach.

Because of the inhibitory effect that lecithin and choline have on the deposition of fat in the liver, these compounds have been used to lower the level of serum cholesterol. Lecithin in large amounts (25 to 40 Gm. per day) will frequently lower the serum cholesterol, but intolerance to this amount of the drug limits its use.

The etiology of atherosclerosis remains unknown, but a mass of clinical and experimental data has accumulated to suggest that it may be a disorder of lipid metabolism. Caloric restriction and exercise within the tolerance of the patient should be encouraged by the physician in an attempt to achieve optimum weight and a normal serum cholesterol value. If the serum cholesterol level still remains high, attempts may be made to lower it with drugs or special diets. However, the drugs and diets are still in their experimental phase and probably should be left to the investigator.

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DANGER OF ALCOHOLISM IN THE TRANSPORTATION INDUSTRY

GUEST EDITORIAL

Marvin A. Block, M.D.

IT HAS been estimated that about 5 million people in the United States suffer from alcoholism. Of these, about 2 million are employed in industry. The cost of this problem, it is claimed, approximates a billion dollars annually. Roughly half of this total is accounted for by loss of time and wages, low productivity, waste of materials, and property damage. The remainder is spent on treating and caring for alcoholic patients, for custody, and, in some cases, punishment and incarceration. The greatest cost, however, cannot be reckoned in dollars; it is reflected in the suffering borne by the patients and by those near and dear to them.

In some cases, the risk and potential loss due to alcoholism goes beyond the patient, or his family and his employer, and involves risk to fellow workers. Where judgment is rendered inaccurate or faulty because of alcoholism, great danger may arise to people with whom the alcoholic works. This may occur with other emotional or mental problems as well. Excessive drinking, however, is tolerated much too far by far too many.

In specific industries, such as common carriers, the loss and suffering as the result of alcoholism may extend to people who are completely unaware of its existence. Here, great responsibility rests on the employer, on the medical departments of these industries, and on industrial and private physicians. Alcoholic bus drivers, locomotive engineers, or airplane pilots not only represent personal peril and risk to their families, employers, and fellow workers but expose countless innocent people to the danger of injury or death. This is true, of course, in all cases of excessive drinking by such employees, even if it has not progressed to the compulsive drinking of alcoholism.

Many workers in the field of alcoholism are aware that in the transportation industry positions of authority and responsibility may be held by alcoholics. There is evidence that in some areas this is recognized by the management of transportation companies and that steps have been taken to aid such persons. Some companies take elaborate precautions to detect excessive drinking among their employees. Some companies have established rehabilitation facilities for treating alcoholic employees. However, in many cases it may be presumed there are many such employees who are working in positions of responsibility without the knowledge of their superiors, though often the facts may be known to some fellow employees, to a private physician, or occasionally to supervisory personnel.

When the facts are known to the patient's personal physician, privileged communication prevents him from reporting them without his patient's consent. How far shall the physician go in respecting this confidence where the safety of the public is at stake? When fellow employees are aware of it, such information is often suppressed in the mistaken notion that it protects the afflicted employee. It might prevent immediate discovery, but at what cost, at what risk?

Alcoholics are subject to emotional tensions, just as anyone else, and in certain circumstances may resort to drinking. Since there is no specific cure for this disease, alcoholics cannot ever safely drink, under any circumstances. They are perpetually susceptible, and with this susceptibility they carry the safety of others for whom they are immediately responsible.

The problem of alcoholism does not represent an extremely prevalent risk in all transportation industries. However, the employment of one alcoholic pilot on a passenger plane might be a much greater risk than the employment of many such people as truck drivers. Some transportation industries are more careful than others in taking precautions against their employees working while under the influence of alcohol. The Committee on Aviation Medicine of the American Medical Association states that precautions in cases of airplane pilots are said to be quite exhaustive. Railroads, bus companies, and trucking lines also have stringent rules regarding drinking by employees. Does this mean, however, that there are no alcoholics employed in these industries as pilots, engineers, or drivers?

We are considering here not drinking per se, but alcoholism, an emotional illness which makes its victims compulsive drinkers. Such patients have been known to circumvent all ordinary precautionary measures and they are resourceful in avoiding detection. Where precautionary measures are taken, it is the responsibility of the medical de-

Chairman, Committee on Alcoholism of the Council on Mental Health, American Medical Association.

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partments of these industries to instigate and follow through on the detection of such persons. This work should not be delegated to employees whose training has not been in this field. The signs and symptoms to be recognized are not necessarily the obvious ones of excessive drinking, or of drinking at all, but of the emotional problems underlying compulsive drinking. Diagnosis of this emotional problem can be made only by trained medical personnel.

It is not suggested that any person be deprived of employment because of emotional illness. It is imperative, however, that those in charge of passenger carriers be carefully observed, examined, and screened to ascertain whether such problems exist. Medical departments of these industries must examine all such personnel with the utmost care, particularly in these emotional areas. Those affected should be suspended from positions of great responsibility until they have completely recovered and are competent to resume work. When positive findings are confirmed to supervisory personnel, this should be mandatory. Signs of emotional instability in personnel should always be reported to medical departments for investigation. With alcoholism, any indication of the disease should be sufficient reason for suspension or a change in position. To treat such matters as mere behavior problems is a form of negligence.

It is obvious that automobile drivers who drink excessively represent a risk on the roads. However, knowingly to allow such drinkers to drive passenger buses, pilot planes, or operate trains is much more reprehensible.

The responsibility for this selection is a matter for the employers and the unions to take firmly in hand. Both must impress on all employees that the public deserves full protection. The way to accomplish this is to educate employers and employees as well as the unions that alcoholism is a treatable disease. The employee must feel secure that he will not be discharged because of his illness, but he must be urged to seek treatment. It is inexcusable for management or a union to withhold or ignore such information when aware of this problem in an employee. If excessive drinking is reasonably suspected, total abstinence should be required, even in borderline cases. Alcohol is not a requirement for healthy living.

Examinations and history taking by medical departments of all transportation industries should be complete and exhaustive. Consent should be given for withdrawal of blood samples for alcohol content at any time. Such measures may be unpopular, but they are necessary. The common carriers should be made completely responsible for seeing that the public is protected.

The entire medical profession has a place in this program to evaluate suspected alcoholics and to treat those authoritatively diagnosed. Medical departments of transportation companies should be adequately manned with understanding personnel. All employees must be encouraged to consult with their employer's medical departments and to report any unusual behavior on the part of any employee. With proper understanding by personnel in these departments, there will be no embarrassment to anyone. With indicated treatment, good recovery, and continued abstinence, such patients can be rehabilitated sufficiently to go back to jobs entailing greater responsibility. The interruption for rehabilitation may require two or three years, during which the patient should be transferred to work involving no risk.

There is no desire to imply that only the carrier industries have the problem of alcoholism. They are selected only because of the risk to the public they are in business to serve. Doubtless there are other industries where similar risks obtain. In the interest of public health, safety, and general welfare, all situations of this nature should be corrected. A cooperative approach by labor, management, and the medical profession is clearly indicated.

THERAPY OF ACUTE INJURIES

Acute injuries and their emergency care are assuming increasing importance to both the physician and the surgeon. Progress which has been made in the treatment of nontraumatic illness, on the one hand, and the frequency of automotive injuries have focused attention on the need for extending scientific information on the management of trauma. Present-day emphasis on drugs, while important, has tended to obscure some of the fundamental principles of treatment of the acutely injured patient, including the rational use of replacement fluids, as well as analgesic, antimicrobial, and immunological agents. Accordingly, the A. M. A. Council on Drugs, in cooperation with the Academy of Medicine of Cleveland and Cuyahoga County Medical Society, Western Reserve University School of Medicine, the Ohio State Medical Association, and the Ohio Committee on Trauma of the American College of Surgeons, is sponsoring a one-day symposium on The Therapy of Acute Injuries to be held in Cleveland, October 7, 1959. The program, which will feature eight authoritative speakers and a question and answer period, is designed to provide practical information on fluid replacement, care of wounds, treatment of burns, antimicrobial therapy, multiple injuries, control of pain, management of fractures, and antitetanus immunization. Physicians are urged to attend this meeting in accordance with the further notice which appears on page 2210 in the Medical News section of this issue of THE JOURNAL.

JOURNAL INDEX

The index to volume 170 of THE JOURNAL will appear in the Sept. 12, 1959, issue. Those who wish extra copies of the index may receive them, without charge, on request to the Circulation and Records Department, American Medical Association, 535 N. Dearborn St., Chicago 10.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

If a fire alarm sounded in your office, clinic, or hospital, you would be alerted instantaneously. Also you would take action instinctively to save your patients and your institution and to extinguish the blaze.

For some time now another type of alarm—political in nature—has been wailing in our ears, alerting the medical profession to the threat of government medicine via the Forand bill. Many physicians have heeded the warning. They have worked individually and collectively to prevent the destruction of the private practice system of medicine and the voluntary health insurance system.

While the alarm has been sounded and directed to every physician in the nation, all too many have refused to recognize the danger or to take action.

In the present struggle with the Forand bill it is not enough to ask: "What is the A. M. A. doing about it?" or "What is my state medical society doing about it?"

Each of us must give our personal effort to the cause of keeping politics and federal bureaucracy out of health care, doctor-patient relations, and medical practice.

For the next 8 to 10 months the threat of federal legislation will be squarely before us. But we dare not wait for weeks and months to act decisively.

Hearings on the Forand bill and the problem of the aged have been held respectively by the House Ways and Means Committee and by the Senate Subcommittee on Problems of the Aged and Aging, Labor and Public Welfare Committee. Everything points to a showdown on this issue in 1960.

We now know our allies. We know we do not stand alone against the Forand measure. In fact, opposition to the bill has come from dozens of corners of society—the American Hospital Association, the American Farm Bureau Federation, the American Association of Retired Persons, the American Pharmaceutical Association, the Chamber of Commerce, the health insurance industry, scores of daily newspapers, the U. S. Department of Health, Education, and Welfare, and many others.

Thus, there is a strong voice and force opposing the proposal. In the ensuing months, however, this group needs to become even more effective. I sincerely believe that all physicians should cooperate with associates and friends in these groups—helping to strengthen the opposition to political medicine.

The very breadth of the support of the Forand bill makes it imperative that physicians in every state conduct a personal campaign in behalf of medicine's position.

As I see it, the task of medicine and its friends will be twofold: (1) to promote and increase all activities and programs for the aged through voluntary and private methods and through community and statewide action and (2) to demonstrate to the American people and to congressional representatives the dangers and pitfalls of government medicine for the elderly or for any segment of the population.

Those who underestimate the threat of this proposed legislation double the responsibilities of their colleagues in meeting the major tasks before the entire profession. Therefore, let none of us be guilty of failing our senior citizens—indeed the entire population—and medicine in this situation.

Louis M. Orr, M.D.
Orlando, Fla.

MEDICAL NEWS

FLORIDA

Dr. Herr Breaks World Fishing Record.—The *St. Petersburg Times* recently reported that Dr. Paul S. Herr, of St. Petersburg, received notice that his catch of a 14-lb. 14-oz. Atlantic Bonito (Sarda Sarda) on 8-lb. test line was accepted as a world record by the National Spin Fishing Association. A certificate concerning the catch made in the Gulf of Mexico May 24 was presented to Dr. Herr, whose catch, the Atlantic Bonito, is not to be confused with the little tuna, commonly called bonito in Florida waters.

ILLINOIS

Meeting of Mental Health Association.—The 50th annual meeting of the Illinois Association for Mental Health will be held at the Hotel Jefferson, Peoria, Friday and Saturday, Sept. 18 and 19. Persons active in mental health are invited. Included in the agenda will be two days of workshop sessions and meetings dealing with aspects of mental health. Persons "nationally prominent in mental health" will speak at the two luncheons on Friday and Saturday. The golden anniversary banquet will be held Saturday night. Host chapter for the meeting will be the Illinois Valley Mental Health Association of Peoria. Illinois reportedly has the second oldest state mental health association in the country. Mr. Gerald M. O'Connor is president of the association. For information, write the Illinois Association for Mental Health, Inc., 209½ E. Adams St., Springfield, Ill.

Chicago

Sir George Pickering to Lecture.—Sir George Pickering, Regius Professor of Medicine at Oxford University, will present "Essential Hypertension—A Quantitative Disease" on Wednesday, Sept. 2, 8 p.m., in the Rothschild Auditorium, Michael Reese Hospital, 2816 S. Ellis Ave. His lecture is presented by the cardiovascular department of the department of medicine.

Celebrate Darwinian Centennial.—An international celebration will be held at the University of Chicago in November to mark the hundredth anniversary of Darwin's theory of evolution. Commemorating the impact of the Darwinian revolution on scientific thought, the celebration will bring together scientists to discuss the evolution of life, man, and the mind in five public sessions on the university campus. Among the guests will be Sir Charles Darwin, former director of the National Physical Laboratory of Great Britain and namesake and grandson of Charles Darwin, and Sir Julian Huxley, grandson of T. H. Huxley, Darwin's great contemporary. The celebration will open Nov. 24, the centennial of the day on which the first edition of the "Origin of Species" was published, and continue through Nov. 29. It is being arranged with the aid of the National Science Foundation and the Wenner-Gren Foundation, and with the cooperation of national scientific societies. Forty-six scientists from eight nations are writing papers about evolution in their fields and suggesting new directions for research. These are background documents for the discussion sessions. The Soviet Union will be represented by G. F. Gause, professor at the Institute of Antibiotics, Academy of Medical Sciences, Moscow. Great Britain, France, Germany, Switzerland, The Netherlands, and Australia also are sending scholars. Sol Tax, professor of anthropology at the University of Chicago, is Chairman of the celebration. A series of panel discussions, each three hours long, will be presented on consecutive days in Mandel Hall. Origin-of-Species Day, Nov. 24, will be formally observed at a dinner sponsored by the Citizens Board of the University of Chicago. The speakers will be Sir Charles Darwin, Chancellor Lawrence A. Kimpton, and Professor Tax. During November the University of Chicago Library will exhibit material relating to Darwin and to the history of evolutionary theory.

MARYLAND

Building Purchased for Basic Science Institution.—Dr. William S. Stone, dean, University of Maryland School of Medicine, Baltimore, announced the purchase of the Hecht Company store at Baltimore and Pine Streets by the University of Maryland. Subsequent to final ratification of the purchase agreement, the acquisition of this store provides additional space for the basic science departments, the division of the physical plant, and certain business offices. The moving of the business and plant departments to the newly acquired structure will release space in the University Hospital for patient care and investigational work. The release of space by the departments of pathology, biochemistry, microbiology, physiology, and pharmacology will provide a large area in the Bressler Building which ultimately will be used by the clinical departments

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

for clinical and fundamental research. Only the department of anatomy is expected not to move immediately into the new structure. While basic instruction in pathology will be carried on in the new building, the postgraduate and routine work will continue in the building at 31 St. Greene St. until the ultimate transfer of facilities to a reconstructed Dental–Pharmacy Building which is to follow the completion of a new Dental School. The acquisition of new space for basic science will afford the School of Medicine an opportunity to place all first- and second-year students under a central laboratory scheme in which the student will be assigned to a central laboratory; will have his own equipment and desk; his own study area; and will remain in the same part of the laboratory during the entire school day.

MICHIGAN

Emergency Team for Radiation Accidents.—A special emergency procedure to handle victims of radiation accidents is being established at the University of Michigan Medical Center, Ann Arbor. A team of specialists, including physicians, surgeons, nurses, medical technicians, and health physicists, will work together to provide prompt diagnosis and treatment for patients exposed to extensive radiation. Dr. William H. Beierwaltes, chief of the U-M clinical radioisotope unit and team coordinator, said the new plan was developed in light of the growing use of radioactive substances by industries and research laboratories throughout Michigan and northern Ohio. Dr. Beierwaltes stressed that plans and training for the emergency team will be based on a rough estimate of "less than a dozen" casualties. The plan is simply a provision for handling the unusual medical problems which might result from the increasing use of radioactive materials. Radiation emergencies will be handled separate from the university's regular Emergency Service because of the different apparatus required and the expected nature of the injury. The victim of a radiation accident will be checked for radioactivity by a Geiger counter at the emergency entrance of the medical center. The first treatment will be a drenching shower to remove any radioactive particles from his body. If the patient is wounded, a surgeon and anesthetist will be on hand to treat him. For several days, samples of the patient's blood, sputum, and urine will be checked for evidence of radiation effects. Doctors will also check for radioactivity in the victim's thyroid, the creases of his skin, his clothing and the vehicle which brought him to the hospital. At the accident scene, physicists will attempt to calculate the exact amount of radiation which the victim might have received.

MISSOURI

Annual Seminar.—The department of medicine of the Menorah Medical Center will hold its annual A. Morris Ginsberg Memorial Seminar Nov. 4-5. The guest this year will be Dr. Morris Ziff, professor of medicine, Southwestern Medical School of the University of Texas, Dallas. All physicians are invited. The general subject will concern rheumatoid arthritis, and the rheumatic diseases. For information, write Dr. Morton C. Creditor, Director, Education and Research, The Menorah Medical Center, 4949 Rockhill Road, Kansas City 10, Mo.

MONTANA

Cancer Clinic in Butte.—The Mary E. Swift Tumor Foundation and members of the Mary E. Swift Tumor Registry & Clinic of St. James Hospital, Butte, will present the fourth Mary E. Swift Memorial Cancer Lecture and Clinic with Drs. Frederick H. Falls, gynecologist, Oak Park, Ill.; Warren C. Hunter, pathologist, Portland, Ore.; Howard J. Tatum, gynecologist, Portland, Ore.; and Alfred Popma, Boise, Idaho, radiologist, and past-president, American Cancer Society, as guest lecturers and clinicians, Saturday, Aug. 29. The subject will be "Cancer of the Cervix and Fundus Uteri."

NEW YORK

New York City

Commemorate Start of Hospital Construction.—Founder's Day, commemorating the start of construction of the new University Hospital of New York University's Medical Center, will take place on Monday, Sept. 28, with Governor Nelson Rockefeller as principal speaker. The new 19-story, 600-bed general hospital will replace the present University Hospital at 303 E. 20th St. and will be the last building to be constructed in the New York University–Bellevue Medical Center 50-million-dollar development program started in 1948. Outdoor ceremonies (under cover) will take place from 4:30 to 5:30 p. m.

Research Training in Psychiatry.—The graduate educational program of the State University of New York Downstate Medical Center offers a two-year program of research training in psychiatry leading to the degree of doctor of medical science. The program is open to physicians who have completed three years of residency in training in psychiatry. Candidates will also be accepted after two years of residency training. In such cases the final year of residency will be taken at the psychiatric division of Kings County Hospital concurrently with this program, and a total of three years will be required to complete the combination of the two-year research training program and the third year of residency. The program provides an opportunity to do research and offers courses concerned with re-

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search methodology in psychiatry. Extensive clinical and laboratory facilities are available for research projects. Each candidate who is accepted will be granted a fellowship of $7,500 for the first postresidency year and $8,000 for the second postresidency year. Three-year candidates will, in addition, receive $7,100 for the final residency year. Applications for the academic year beginning September, 1960, should be submitted before Jan. 1, 1960. Application forms and information may be obtained by writing the Office of Admissions, Downstate Medical Center, 450 Clarkson Ave., Brooklyn 3.

NORTH CAROLINA

Dr. Sulkin Named Anatomy Chairman.—Norman M. Sulkin, Ph.D., professor of anatomy, was named chairman of the department of anatomy at Bowman Gray School of Medicine. Dr. Sulkin has served as acting chairman for the past year.

Personal.—Dr. Ewald W. Busse, Durham, director of the Duke University Center for the Study of Aging, was appointed to head the Committee on Medical Research in Gerontology for the 1961 White House Conference on Aging.——Dr. Kenneth L. Pickrell, professor of plastic surgery at Duke University Medical Center, Durham, was chosen to direct the third International Congress of Plastic Surgeons, scheduled for 1963 in the United States. Held every four years, the meetings bring together plastic surgeons from throughout the world for a week of scientific and professional sessions. The 1963 congress is tentatively scheduled for New York in the fall.

PENNSYLVANIA

Philadelphia

Surgical Society Meeting.—The Hawthorne Surgical Society, an honorary fellowship of the surgical classes of the Graduate School of Medicine of the University of Pennsylvania, will hold its eighth annual meeting on Tuesday evening, Sept. 29, in Atlantic City, Shelburne Hotel. An outstanding event will be the presentation of a valuable award given for "distinguished service in surgical education." The award will be made in conjunction with the meeting of the American College of Surgeons in Atlantic City. Reservations for dinner are to be sent to Dr. Alfred S. Frobese, 255 S. 17th St., Philadelphia 3. Cost for the dinner is $10 per plate.

Rehabilitation Center Dedicated.—The George Morris Piersol Rehabilitation Center was dedicated June 16 at the Hospital of the University of Pennsylvania. Named for Dr. George Morris Piersol, emeritus professor of physical medicine and rehabilitation, University of Pennsylvania School of Medicine, and former dean of the Graduate School of Medicine, the $600,000 center "provides the latest types of equipment and facilities for rehabilitation treatment and therapy." Dr. Howard A. Rusk, director of physical medicine and rehabilitation at New York University-Bellevue Medical Center, spoke at the dedication. The new center is both a patient service and a training unit, with comprehensive training programs in physical therapy, occupational therapy, speech therapy, vocational counselling, social services, and psychological testing of physically handicapped persons. Since the establishment of a rehabilitation center program in 1954, in the old building unit of the New Piersol Center, 529 patients have completed the rehabilitation program, and have been "graduated." The new facilities will make it possible to double the number being treated, although the inpatient capacity will remain at 20. Features of the building include a gymnasium for physical therapy, occupational therapy, and recreation activities; a kitchen, equipped for the preparation of inpatient meals

The George Morris Piersol Rehabilitation Center.

and special diet preparations; class rooms; offices; and improved housing facilities for patients. It also includes a controlled climate chamber for studying the effects of temperature, barometric pressure, ionization, humidity, and other atmospheric phenomena on disease. This unit, which will be opened in the fall of this year will be a completely self-contained patient unit, devoted to research. Funds for the center were provided by private donors and the federal government under the Hill-Burton Act.

SOUTH CAROLINA

Clinical Assembly in Clemson.—The 24th annual Piedmont Post Graduate Clinical Assembly will be held Sept. 16-17 at Clemson House, Clemson. The program includes the following speakers: Drs. Claude Starr-Wright, Augusta, Ga.; William C. Thomas, Gainesville, Fla.; Delbert M. Bergenstal, Bethesda, Md.; Euclid G. Herndon, Atlanta, Ga.;

Harris D. Riley Jr., Oklahoma City, Okla.; Elbert T. Tuttle Jr., Atlanta, Ga.; Cyril Y. Bowers, New Orleans; George V. Irons Jr., Donaldson Air Force Base Hospital; and Robert P. Grant, Bethesda, Md. For information write Dr. William Schulze, 7 Sumner St., Greenville, S. C.

TEXAS

Drs. Hansen and Wiese to Retire.—Dr. Arild E. Hansen, chairman, department of pediatrics, and Hilda F. Wiese, Ph.D., professor of pediatric research, will retire from the School of Medicine of The University of Texas Medical Branch, Galveston, Sept. 1. Dr. Hansen has accepted the position of director of research of the Bruce Lyon Memorial Research Laboratory, affiliated with the Children's Hospital of the East Bay, Oakland, Calif., and Dr. Wiese has accepted the position of director of laboratories at the same institution.

WISCONSIN

Dr. Pfeifer Day.—Residents of New London set aside June 6 to honor Dr. Fred J. Pfeifer "in appreciation of his 50 years of devoted service to the community" by celebrating "Dr. Pfeifer Day." A parade was held in the afternoon followed by a "This is Your Life" program and a dinner in the evening. Dr. Pfeifer came to New London in November, 1909. He began by setting up a five-room hospital in his home in 1922. This lasted for 20 years. In 1931 a 50-bed community hospital was opened to patients largely through the efforts of Dr. Pfeifer and other residents.

GENERAL

Advance Date for Pharmacopeia Convention.—The decennial meeting of the U. S. P. Convention will be held on Tuesday and Wednesday, March 29 and 30, 1960, with a preliminary conference on Monday, March 28. The U. S. P. board of trustees has thus advanced the meeting by two weeks, in order to eliminate a conflict with two simultaneous meetings, namely: the Federation of American Societies for Experimental Biology and the American Chemical Society. Hotel facilities are still available, and the meeting will be held at the Statler Hilton in Washington as planned. As previously noted, credential forms will be issued this fall.

World Medical Meeting in Montreal.—The 13th general assembly of the World Medical Association will be held Sept. 6-12 at the Queen Elizabeth Hotel, Montreal, with His Royal Highness, Prince Philip, Duke of Edinburgh, president of the Canadian Medical Association, as patron. A medical editors' conference is planned for the afternoon of Sept. 7. The presidential address will follow the election and installation of the 1959-1960 president, with Dr. L. R. Mallen, chairman of the council presiding and conducting the installation ceremonies. The keynote address will be given by Dr. Norman H. Gosse, Halifax, N. S. A panel discussion, "The North American Approach to Health Insurance," moderated by Dr. Joseph A. McMillan, Charlottetown, Prince Edward Island, Canada, will be preceded by committee reports. Election of the president-elect, treasurer, and members of the council will precede the final orders of business. For information, write Dr. Louis H. Bauer, Secretary-General, World Medical Association, 10 Columbus Circle, New York 19.

Allergy Month.—The Allergy Foundation of America, a national nonprofit, voluntary health agency, which unites the public, the medical profession, research scientists, and health workers "in a common effort to conquer the allergic diseases," sponsors National Allergy Month (Aug. 15 to Sept. 15), and will conduct an intensive campaign of public information and education through the press, radio, and TV. A free education pamphlet is prepared each year for National Allergy Month. The foundation supports research and training, and its address is the Allergy Foundation of America, 801 Second Ave., New York 17.

Oct. 7 Symposium on Acute Injuries.—The council on Drugs of the American Medical Association, in cooperation with the Academy of Medicine of Cleveland and Cuyahoga County Medical Society, the Western Reserve University School of Medicine, the Ohio State Medical Association, and the Ohio Committee on Trauma of the American College of Surgeons, will present a symposium, "The Therapy of Acute Injuries," in the auditorium of the Alen Memorial Medical Library, 2009 Adelbert Road, Cleveland, on Wednesday, Oct. 7. All physicians, including graduate and undergraduate students of medicine are cordially invited to attend this one-day program, which will feature eight outstanding speakers and a question-and-answer period, on various aspects of the management of traumatic lesions. The program is scheduled to begin at 10 a. m. Registration, which is free, at 9:30 a. m. Advance reservations for a buffet luncheon to be held at 1 p. m. in the Auditorium at $2.50 each, should be forwarded, with remittance, to Mr. Robert A. Lang, Executive Secretary, Academy of Medicine of Cleveland, at the above address, on or before Oct. 1. The symposium is acceptable for five hours of category II credit for members of the American Academy of General Practice.

Traffic Deaths Increase.—Traffic across the nation took a toll of 17,090 lives in the first six months of 1959, the National Safety Council reported. This was 5% more than last year, when the six-month toll was 16,280. Travel also increased 5% in the first half of the year. Thus, despite the increase in deaths, the mileage death rate was the same for the six months as it was for the comparable period last

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year—5.1. This is the lowest rate on record for a similar period. The council estimated that disabling injuries from traffic accidents in the first half of the year totalled 600,000. June brought a 5% increase in traffic deaths—3,150 this year against 3,000 last year. It was the sixth straight month to show an increase over the corresponding month a year ago. The increase in deaths is occurring principally in rural areas, the council said. In June rural deaths were up 6% while urban deaths increased only 1%. For the six-month period, rural deaths rose 6%, while urban deaths were up 3%. Of the 810 increase in deaths in six months, about 700 of them occurred in rural areas.

Joint Pathology Meeting.—Pathologists will take a course in "Management Skills" Sept. 6 at which businessmen will be the teachers. The one-day course, conducted by the College of American Pathologists, will be held in connection with the society's joint annual meetings with the American Society of Clinical Pathologists at the Palmer House, Chicago, Sept. 7-11. Dr. Arthur H. Dearing, Chicago, executive director of the college, is in charge of arrangements. Dr. Charles P. Larson, Tacoma, Wash., president of the college, will serve as chairman of the general sessions. Four panel discussions are planned with the following moderators:

Fluorescent Antibody Techniques, Dr. George P. Blundell, Frederick, Md.
Coagulation Techniques, Dr. John R. Carter, Iowa City.
Pathology Service for Ambulatory Patients, Dr. William J. Reals, Wichita, Kan.
Problems of Setting-up a Private Laboratory—How to Do It, Dr. Melvin L. Sommer, Beverly Hills, Calif.

Open meetings of selected committees of the college will begin at 4 p. m., Sept. 7, and a business meeting will be held at 8 p. m. For information, write Dr. A. H. Dearing, Executive Director, College of American Pathologists, Prudential Plaza, Chicago 1.

Group to Study Fund Appeals.—The American Heart Association announced that it would seek the appointment of "an impartial group of physicians, scientists, and community leaders" to study the problems arising from the increasing number of fund appeals by health agencies. Dr. Francis L. Chamberlain, San Francisco, president of the association, said the intent of the proposed study would be "to create better understanding of the primary health needs of the nation, and at the same time to provide a yardstick for adequate and intelligent support of those health causes which are of greatest concern to the greatest number of people." Approval was given by the association's board of directors to a resolution calling for the appointment of the study group. According to the resolution, the proposed committee would (1) define the major areas of chronic disease that threaten the nation's health and well-being and (2) set up standards by which potential contributors and volunteers could evaluate the health causes which seek their support.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	Aug. 1, 1959 Paralytic Type	Aug. 1, 1959 Total Cases	Aug. 2, 1958 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	3	3	1
Rhode Island	..	..	..
Connecticut	6	13	9
Middle Atlantic States			
New York	3	7	11
New Jersey	2	4	7
Pennsylvania	3	5	4
East North Central States			
Ohio	2	4	5
Indiana	9	14	5
Illinois	3	5	5
Michigan	2	15	26
Wisconsin	1	2	2
West North Central States			
Minnesota	6	7	..
Iowa	6	22	3
Missouri	15	31	3
North Dakota	..	..	3
South Dakota	..	..	1
Nebraska	6	9	..
Kansas	2	17	17
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	2
District of Columbia	..	..	..
Virginia	9	10	7
West Virginia	2	2	1
North Carolina	6	8	3
South Carolina	2	7	..
Georgia	2	3	..
Florida	3	3	5
East South Central States			
Kentucky	..	..	..
Tennessee	11	12	6
Alabama	11	12	5
Mississippi	5	6	7
West South Central States			
Arkansas	18	22	..
Louisiana	2	5	3
Oklahoma	3	5	8
Texas	17	25	16
Mountain States			
Montana	1	1	2
Idaho	..	..	..
Wyoming	..	..	..
Colorado	1	1	..
New Mexico	..	..	2
Arizona	1	2	1
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	6	2
Oregon	6	6	3
California	9	13	8
Alaska	5	5	..
Hawaii	..	..	3
Territories and Possessions			
Puerto Rico	..	..	2
Total	163	312	164

LATIN AMERICA

Congress on Obstetrics and Gynecology in Venezuela.—The second Venezuelan Congress on Obstetrics and Gynecology will be held in Caracas, Feb. 19-24, 1960. The congress is being organized to celebrate the 20th anniversary of the Obstetrical and Gynecological Society of Venezuela. Main subjects will be as follows:

Obstetrics
1—Anemia in Obstetrics.
2—Induction of Labor.
3—Perinatal Mortality.
4—Evaluation of Thierry's Spatules.

Gynecology
1—Pathology of the Tubes.
2—Early Diagnosis of Cancer of the Cervix.
3—Laparoscopy.
4—Gynecography.

Round-table discussions will include Anemia in Obstetrics, Induction of Labor, Perinatal Mortality, Pathology of the Tubes, and Amenorrhea. For information, write Dr. H. Marcane Guzmán, Apartado 7332 (San Martin), Caracas, Venezuela, Congress Secretary.

FOREIGN

History of Science Congress.—The ninth International Congress of the History of Science and the Spanish Association for the History of Science will be held in Barcelona and Madrid, Spain, Sept. 1-7. Subjects to be followed by free discussions include the following:

Scientific Relations Between the Eastern and Western World.
Development of Science in Medieval Europe, Particularly in the 14th and 15th centuries.
Scientific Education in America and Its Relations to Europe.
Recent Research Work in the Field of History of Mathematical and Physical Science in Europe from the 16th to the 18th Century.
Evolution of Classical Medicine and Biology to the Middle Ages and from there to Modern Times.
Towards the Origins of Naval Cartography.

Lectures will be grouped in the following sections: history of (1) techniques and applied science; (2) biology and medicine; (3) mathematics, physics, and astronomy; (4) chemistry and pharmacy; (5) geography and geology; and (6) science in general. Lectures will be presented in Spanish, French, English, and German. For information, write Prof. Dr. Juan Vernet, Facultad de Letras, Universidad, Barcelona.

University of Edinburgh Reviews Medical Curriculum.—The potential advantages or disadvantages of reduced lecture time and increased clinical experience in medical training are being reviewed by the University of Edinburgh, Scotland. A Rockefeller Foundation grant will enable faculty members to observe medical education programs in other countries and to discuss possible changes in the Edinburgh program at several conferences. The University of Edinburgh is a center of medical training for students from the newer members of the British Commonwealth and from other African and Asian countries. To give these students as well as those from the British Isles, the "best possible" training, the university is both examining its curriculum and exploring the relationships between students' performance in medical school and their family, school, and social background.

Convention on Nutrition.—The fifth International Convention on Nutrition and Vital Substances will be held Oct. 7-11 at Constance, Germany, and Zurich, Switzerland, sponsored by the International Society of Research on Nutrition and Vital Substances. Following the plenary session Oct. 7, the program will include the following session titles:

Biological Cycle: Soil-Plant-Animal-Human Being.
The Medical Man on the Nutritional and Environmental Problems of Juveniles.
Water, Dietary and Cooking Salts.
Radiation: Physical-Biological-Medical.
Disturbance of the Radiation Potential by Artifical Atomic Fission.
Milk-Bread-Cereals.
The General Position Regarding Toxic Substances, a Cause of Civilization's Diseases.
Cancer—A General Disease.
The Tooth—Part of the Biological Entity.
Caries—Predominantly Induced by Civilization.
Reform of Nutrition.

The conference language is German and simultaneous translation into English and French will be established. The International Society of Research on Nutrition and Vital Substances is a union of medical and natural sciences and includes in its membership doctors, agricultural scientists, and allied scientific and academic professions. For information, write the Secretariat whose address is Hannover-Kirchrode, Bemeroder Strauss 61, Germany.

Course on Gastric Diseases in Czechoslovakia.—With the 18th course, held in Carlsbad in 1957, the Czechoslovakia Physiatric Society resumed the prewar tradition of its Carlsbad courses. The society is organizing the 19th International Post-Graduate Medical Course again in Karlovy Vary/Carlsbad/, Sept. 14-19. The main theme will be "Gastric Diseases," and free themes from different branches of medical science will be presented. Papers will be read by research workers from Belgium, Bulgaria, England, Egypt, Finland, France, Germany, Hungary, Italy, Poland, Rumania, Soviet Union, Sweden, and Czechoslovakia. The official languages are English, French, Russian, German, Slovak, and Czech. There will be simultaneous interpreting of these languages. The program will be complemented by excursions and cultural and social events. Immediately after this course the Czecho-

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slovak Society of Gastroenterology and Nutrition is organizing its congress with international participation from Sept. 21-24, also in Carlsbad. The main themes of this congress are: (1) Infectious Hepatitis, (2) the Importance of Fats in Nutrition, and (3) the Surgical Treatment of Obstructive Jaundice. For application and inquiries apply to the Czechoslovak Physiatric Society, Albertov 7, Prague 2, Czechoslovakia.

CORRECTION

Cholestasis.—In the clinical note "Cholestasis due to Prochlorperazine," by Weinstein et al. (in THE JOURNAL, Aug. 1) the albumin level given in the fifth line on page 1664 should have been 4.1 Gm. per 100 cc.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations, July 8, 1960. Final date for filing application is January 8. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Written.* Several Cities, Oct. 5. *Oral.* Oklahoma City, Jan. 15-18, 1960. The final date for filing all applications was July 1, 1959. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *1959 Schedule—Written,* Oct. 19. Final date for filing application was May 1. *Oral.* For candidates on the West Coast, Portland, Ore., Sept. 9-12. Final date for filing application was March 1. *Oral.* For candidates on the East Coast, Nov. 6-7, 9-10. Final date for filing application was March 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. New Haven, Nov. 14-16. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Applications for certificates, new and reopened, Part I, and requests for re-examination Part II are now being accepted. *Part I. Written.* Jan. 15, 1960. Deadline date for receipt of applications was August 1, 1959. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* St. Louis, Oct. 6-10. *Written.* January 1960 in various cities. Applications for the 1960 written examination must be filed before July 1. *Oral.* 1960, San Francisco, May; Chicago, October. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* Chicago. Jan. 19-21, 1960. The deadline for the receipt of application was Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral.* Chicago, Oct. 5-9. Final date for filing application was April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: New Orleans, Nov. 12-14. Final date for filing application is October 1. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PATHOLOGY: *Examination in Forensic Pathology.* New Orleans, Nov. 13. Final date for filing application is October 1. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Chicago, Oct. 9-11. *Written.* January 1960. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* Miami, Fla., Oct. 15-17. Final date for submitting case reports was July 1. Corresponding Secretary, Miss Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, September. Final date for filing application was March 15. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Chicago, Oct. 19-20; New York, Dec. 14-15; San Francisco, Mar. 14-15, 1960. Training credit for full time psychiatric and/or neurologic assignment in unapproved military programs or services between the dates of Jan. 1, 1950 and Jan. 1, 1954 was terminated on Jan. 1, 1959. Sec., Dr. David A. Boyd, 102-110 Second Ave. S. W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Examination.* Washington, Dec. 6-9. Deadline for filing application was July 1. Candidates examined in Diagnostic Roentgenology may expect to be examined in Physics. Obligatory examination in Nuclear Medicine has been postponed until after June 30, 1962 for those candidates being examined in Radiology or Therapeutic Radiology. Until that time the examination in Nuclear Medicine will be optional for those who wish to be examined in Radiology or Therapeutic Radiology. *Examination.* Cincinnati, Spring 1960. Deadline for filing applications is Jan. 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written* examinations (Part 1) will be held on December 2, 1959 at various centers to be announced later. Candidates are urged to apply several months before completion of training requirements although the closing date for filing applications is August 1. Those completing training requirements after September 30 cannot be considered for the Part I examination in December of the same year. *Oral examinations (Part II):* Chicago, Sept. 14-15; Seattle, Sept. 17-18; Baltimore, Oct. 19-20; Cincinnati, Nov. 9-10; Boston, Dec. 14-15; Winston-Salem, No. Car., Jan. 18-19; New York, N. Y., Feb. 15-16; New Orleans, Mar. 14-15; Kansas City, Kans., May 16-17, and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, September 1959. Final date for filing application was July 1. *Oral.* September. Final date for filing application was July 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2, Mich.

AMERICAN BOARD OF UROLOGY: *Written.* Approximately 25 cities throughout the country, December 4, 1959. *Oral-Clinical* and *Examination in Pathology.* Chicago, February 1960. Final date for filing application is Sept. 1, 1959. Sec., Dr. William Niles Wishard, 30 Westwood Rd., Minneapolis 26, Minn.

DEATHS

Ackley, David Bartine ⊛ Trenton, N. J.; Baltimore Medical College, 1901; fellow of the American College of Surgeons; retired chief of staff at Mercer Hospital, where a medical library is named in his honor, and where he died June 14, aged 83.

Anderson, Reuben Mauritz ⊛ Hackensack, N. J.; University of Minnesota Medical School, Minneapolis, 1925; veteran of World War I; fellow of the International College of Surgeons and the American College of Surgeons; member of the American College of Chest Physicians and the American Trudeau Society; interned at the Ancker Hospital in St. Paul and the Hackensack (N. J.) Hospital; received a postgraduate fellowship at the Mayo Foundation in Rochester, Minn.; director of surgery at the Bergen Pines County Hospital in Paramus and the Hackensack (N. J.) Hospital; died in Paramus June 14, aged 62, while golfing.

Barbrow, Abraham L. ⊛ Pittsburgh; Jefferson Medical College of Philadelphia, 1919; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; past-president of the Pittsburgh Pathology Society; director of the pathology department at Homestead (Pa.) Hospital, where he died June 11, aged 63.

Barclay, Watt ⊛ Woodville, Texas; University of Tennessee College of Medicine, Memphis, 1932; member of the American Academy of General Practice; formerly mayor; served as president of the Tyler County Medical Society; formerly county health officer; associated with the Tyler County Hospital, where he died June 10, aged 61.

Bardsley, William James, Park City, Utah; Rush Medical College, Chicago, 1903; associated with the Park City Hospital; veteran of World War I; died in Salt Lake City June 7, aged 89.

Barrow, Bernard ⊛ Blackstone, Va.; University of Maryland School of Medicine, Baltimore, 1897; veteran of World War I; died June 13, aged 84.

Beebe, Leslie Walter ⊛ Oak Park, Ill.; Chicago Homeopathic Medical College, 1897; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; past-president of the Aux Plaines Branch of the Chicago Medical Society; served as health officer; on the staff of the West Suburban Hospital; died June 19, aged 86.

⊛ Indicates Member of the American Medical Association.

Berrie, Lloyd Harvey ⊛ Caribou, Maine; Tufts College Medical School, Boston, 1934; interned at the Worcester (Mass.) City Hospital; died in Jonesport June 5, aged 56.

Bickford, Wallace Mellen ⊛ South Miami, Fla.; Tufts College Medical School, Boston, 1905; practiced in Marshall, Mo., where he was past-president of Saline County Medical Society and on the staff of John Fitzgibbon Memorial Hospital; served as Selective Service examiner during World War II and was an authorized medical examiner for the Civil Aeronautics Administration; died in the Mercy Hospital, Miami, June 14, aged 79.

Blair, Samuel F., Dallas, Texas; Fort Worth School of Medicine, Medical Department of Fort Worth University, 1909; died June 5, aged 89.

Braude, Morris ⊛ Chicago; Rush Medical College, Chicago, 1905; served on the faculty of his alma mater and the University of Illinois College of Medicine; specialist certified by the American Board of Psychiatry and Neurology; attending psychiatrist at the Cook County Psychopathic Hospital; author of "Principles and Practice of Clinical Psychiatry"; died June 18, aged 75.

Brighton, Archibald Wilson, Wyandotte, Mich.; Michigan College of Medicine and Surgery, Detroit, 1900; associated with the Wyandotte General Hospital and in 1950 the staff honored him with a gold-framed medical service scroll and an honorary life membership in recognition of his long years of service; formerly city health commissioner; died May 28, aged 80.

Carey, Mitchel Daniel ⊛ Ludlow, Vt.; University of Vermont College of Medicine, Burlington, 1914; served as a member of the school board; veteran of World War I; health officer; associated with Springfield (Vt.) Hospital and the Rutland (Vt.) Hospital, where he died June 8, aged 72.

Chesnutt, Thomas Henry, Adel, Ga.; Emory University School of Medicine, Atlanta, 1915; veteran of World War I; served as health officer of Colquitt County; for many years on the staff of the State Hospital in Milledgeville; died in the Memorial Hospital June 2, aged 76.

Childress, Marmion Hugo ⊛ San Francisco; University of California School of Medicine, San Francisco, 1921; head physician and surgeon at the Preston School of Industry in Ione, Calif.; died in June, aged 66.

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Daffinee, Ralph Weir ⊛ Melrose, Mass.; Harvard Medical School, Boston, 1928; certified by the National Board of Medical Examiners; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; served as chairman of the school committee; on the faculty of his alma mater and Tufts College Medical School in Boston; associated with the Massachusetts General Hospital in Boston, Malden (Mass.) Hospital, and the Melrose Hospital; died in the Peter Bent Brigham Hospital in Boston June 21, aged 56.

Damiani, Joseph, Phoenix, Ariz.; Jenner Medical College, Chicago, 1900; formerly practiced in Chicago, where he was on the staff of the Columbus Hospital; died June 11, aged 86.

Davis, Jesse James ⊛ Higgins, Texas; Atlanta College of Physicians and Surgeons, 1902; served as president of the Higgins Lions Club; died June 13, aged 85.

Dewhirst, William Hamer Jr. ⊛ Merced, Calif.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1947; past-president of the Merced County Tuberculosis and Health Association; member of the American Academy of General Practice; associated with the Merced County General Hospital and the Mercy Hospital, where he died in the doctors' lounge June 2, aged 43.

Dryden, Franklin Morton, Pasadena, Calif.; the Hahnemann Medical College and Hospital, Chicago, 1907; died in the Greenbrier Sanitarium June 12, aged 79.

Dunning, Lehman M. ⊛ Indianapolis; Indiana University School of Medicine, Indianapolis, 1908; member of the American Academy of General Practice; veteran of World War I; served on the faculty of his alma mater; associated with the Methodist and St. Vincent's hospital; died June 3, aged 75.

Dupin, Eugene Angot ⊛ New York City; Columbia University College of Physicians and Surgeons, New York City, 1910; died May 2, aged 77.

Edwards, William Cornelius, Rogers, Ark.; Kansas City (Mo.) College of Medicine and Surgery, 1928; died June 5, aged 54.

Ellis, Francis Duffy, New Britain, Conn.; University of Pennsylvania School of Medicine, Philadelphia, 1918; served as city school physician and Farmington health officer; physician at the E. C. Goodwin Technical School; at one time a medical missionary in India; associated with the New Britain General Hospital; died June 9, aged 67.

Estes, Henry Grady ⊛ Atlanta, Ga.; Atlanta College of Physicians and Surgeons, 1913; died in the Crawford W. Long Memorial Hospital June 6, aged 68.

Field, Henry ⊛ Herkimer, N. Y.; Albany (N. Y.) Medical College, 1896; associated with the Herkimer Memorial Hospital; died June 5, aged 93.

Finesinger, Jacob Ellis ⊛ Baltimore; born in New Castle, Pa., Oct. 28, 1902; Johns Hopkins University School of Medicine, Baltimore, 1929; specialist certified by the American Board of Psychiatry and Neurology, Inc.; certified by the National Board of Medical Examiners; professor of psychiatry at the University of Maryland School of Medicine and College of Physicians and Surgeons; from 1936 to 1949 assistant professor of psychiatry at Harvard Medical School in Boston; member of the American Society of Clinical Investigation, American Neurological Association, American Psychoanalytic Association, American Psychosomatic Society, American Psychiatric Association, and Association for Research in Nervous and Mental Diseases; consultant in neuropsychiatry for the U. S. Public Health Service and a member of the medical advisory board of the Selective Service System; member of the National Research Council; chief psychiatrist at the University Hospital; served on the staff of the Massachusetts General Hospital and as consultant in psychiatry at the Massachusetts Eye and Ear Infirmary in Boston; consultant for the Veterans Administration; died in the University Hospital June 19, aged 56.

Finkle, Beverly Arthur ⊛ Lincoln, Neb.; Chicago College of Medicine and Surgery, 1913; fellow of the International College of Surgeons; past-president of the Lancaster County Medical Society; physician for the Nebraska Penitentiary; formerly assistant superintendent at the State Hospital in Norfolk and superintendent of the Nebraska Orthopedic Hospital; died June 24, aged 75.

Flanagan, Oscar Alvin, Denver; Kentucky University Medical Department, Louisville, 1904; died June 3, aged 79.

Flickinger, Roger Richard ⊛ Mason City, Iowa; State University of Iowa College of Medicine, Iowa City, 1927; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World War II; associated with the Park Hospital and St. Joseph's Mercy Hospital; died June 10, aged 58.

Freeman, Alexander Sanford ⊛ Chicago; University of Illinois College of Medicine, Chicago, 1930; associated with Alexian Brothers Hospital, where he died June 22, aged 55.

Freile, Eva, Jersey City, N. J.; Woman's Medical College of Pennsylvania, Philadelphia, 1912; died in the Pinehaven Nursing Home and Sanitarium in Pinewald April 22, aged 72.

Fuller, Harvey Lewis ⊗ Baltimore; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1938; interned at the Chester (Pa.) Hospital and the Sinai Hospital in Baltimore, where he served a residency; specialist certified by the American Board of Internal Medicine; associated with Sinai, Johns Hopkins, Doctors, Lutheran, and Maryland General hospitals; died in Atlantic City June 9, aged 45, while attending a meeting of the American Medical Association.

Hagen, Spencer ⊗ Cincinnati; Eclectic Medical College, Cincinnati, 1929; fellow of the International College of Surgeons; president-elect of the Cincinnati Surgical Society; veteran of World War II; associated with the McCormick Hospital in Oxford, Ohio, St. Mary's and Mercy hospitals; chief of the surgery department of the Bethesda Hospital; a member of the board of commissioners of Hamilton County; formerly served as city police and fire surgeon; died June 21, aged 55.

Hanna, John Marvin, Upper Darby, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1902; died in the Hahnemann Hospital, Philadelphia, June 7, aged 78.

Haughey, George Cornelius, Prescott, Kan.; Loyola University School of Medicine, Chicago, 1916; died in the University of Kansas Medical Center in Kansas City, June 5, aged 67.

Hayward, Muriel Valentine, Coral Gables, Fla.; Columbia University College of Physicians and Surgeons, New York City, 1926; interned at the New York Infirmary for Women and Children in New York City; formerly located in Winnetka, Ill.; awarded the French Croix de Guerre for her services in World War I; died June 11, aged 74.

Higbee, Arthur Lloyd ⊗ Detroit; Rush Medical College, Chicago, 1927; died in the Harper Hospital June 10, aged 58.

Jackson, Luke Bunyan ⊗ San Antonio, Texas; University of Texas School of Medicine, Galveston, 1908; member of the American Academy of General Practice and was first president of the Bexar County chapter; past-president of the Bexar County Medical Society; associated with the Nix Memorial Hospital, Santa Rosa Hospital, and the Baptist Memorial Hospital, where he died June 3, aged 74.

Jacotel, Joseph A. ⊗ Milbank, S. D.; Laval University Medical Faculty, Montreal, Que., Canada, 1898; past-president of the Grant County Medical Society; served as county coroner and chairman of the city board of health; associated with St. Bernard's Providence Hospital, where he died June 5, aged 84.

Keith, Freeman E. ⊗ St. Bernice, Ind.; Medical College of Indiana, Indianapolis, 1897; served on the staff of the Reid Memorial Hospital in Richmond, Ind.; died June 6, aged 86.

Kersten, Werner Karl, Detroit; Loyola University School of Medicine, Chicago, 1919; at one time county medical examiner; on the staffs of the Cottage Hospital, Grosse Pointe, Mich., East Side General, Woman's, and St. Joseph Mercy hospitals, and the Detroit Memorial Hospital, where he died June 9, aged 64.

King, Frank Aylsworth Sr., Benton Harbor, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; served on the staff of the Memorial Hospital in St. Joseph and the Mercy Hospital, where he died June 7, aged 79.

Krauskopf, Henry ⊗ Flushing, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1902; fellow of the American College of Surgeons; served on the faculty of the New York Polyclinic Medical School and Hospital; associated with the Jewish Memorial Hospital in New York City, where he was past-president of the medical staff; died in Atlantic City, N. J., June 18, aged 78.

Kretschmer, Otto Sheibel ⊗ Denver; University of Colorado School of Medicine, Denver, 1920; fellow of the American Society of Clinical Pathologists; on the courtesy staff of the St. Luke's Hospital, where he died June 6, aged 70.

Kunkelman, Donald Reed, Canonsburg, Pa.; Baltimore Medical College, 1900; veteran of World War I; died in the Canonsburg Hospital June 2, aged 81.

Lane, Myrven Alonzo ⊗ Orland Park, Ill.; Northwestern University Medical School, Chicago, 1941; interned at the Englewood Hospital in Chicago, where he was a member of the staff, and where he died June 25, aged 64.

Landrum, Marvin McTyre ⊗ Lampasas, Texas; St. Louis University School of Medicine, 1907; veteran of World War I; county health officer; died in the King's Daughters Hospital, Temple, June 3, aged 74.

Leinfelder, Mary Jane Tenney, Iowa City, Iowa; University of Wisconsin Medical School, Madison, 1929; died May 4, aged 56.

Levy, Daniel Frederick ⊗ New Haven, Conn.; Yale University School of Medicine, New Haven, 1919; past-president of the New Haven County Medical Society and the New Haven Medical Association; member of the American College of Gastroenterology and the Industrial Medical Association; served on the staff of the Grace–New Haven Community Hospital; died in the Hospital of St. Raphael June 13, aged 66.

Lewis, Eli Alfred, New York City; Long Island College Hospital, Brooklyn, 1921; died March 7, aged 60.

Lyman, Richard Sherman, Montclair, N. J.; born in Hartford, Conn., Jan. 29, 1891; Johns Hopkins University School of Medicine, Baltimore, 1921; specialist certified by the American Board of Psychiatry and Neurology; member of the American Neurological Association; served on the faculty of his alma mater, Meharry Medical College in Nashville, Tenn., and Duke University School of Medicine in Durham, N. C.; formerly associate professor of medicine at the University of Rochester School of Medicine and Dentistry in Rochester, N. Y.; spent the year 1930-1931 at the Institute of Experimental Medicine in Leningrad with Pavlov in the department of physiology; in 1931 became associate professor of psychiatry at the National Medical School in Shanghai and from 1932 to 1937 held that position at Peiping Union Medical College; veteran of World War I; during World War II served in Washington, D. C., Ceylon, and China as a major in the Office of Strategic Services; at one time on the staff of the Strong Memorial Hospital in Rochester, N. Y.; died June 13, aged 68.

MacMillan, Andrew Louis ⊛ Concord, N. H.; Harvard Medical School, Boston, 1909; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; past-president of the New England Ophthalmological Society; past-vice-president of the New England Otological and Laryngological Society; on the staff of the Concord Hospital, where he died June 8, aged 76.

Marsh, Anthony Wayne, Sanford, Fla.; University of Vermont College of Medicine, Burlington, 1911; died June 2, aged 74.

Maul, Robert Franz ⊛ Denver; University of Colorado School of Medicine, Denver, 1920; member of the American Academy of General Practice; died in the Presbyterian Hospital June 9, aged 73.

Mayer, Edward Everett ⊛ Pittsburgh; born in Allegheny, Pa., June 18, 1876; Western Pennsylvania Medical College, Pittsburgh, 1897; specialist certified by the American Board of Psychiatry and Neurology, Inc.; member of the American Academy of Neurology, American Psychiatric Association, Association for Research in Nervous and Mental Diseases, American Psychopathological Association, and the Central Neuropsychiatric Association; associate professor emeritus of psychiatry at the University of Pittsburgh School of Medicine; associated with South Side, Woman's, and Montefiore hospitals; director of psychiatry, Allegheny County Behavior Clinic; on the consulting staff of the Presbyterian Hospital, where he died June 2, aged 82.

McGarrahan, John Cooley, Cohoes, N. Y.; Harvard Medical School, Boston, 1921; an examining physician in the New York State Department of Workmen's Compensation; associated with the Cohoes Memorial Hospital; died June 4, aged 62.

Meise, August Herman, New York City; Fordham University School of Medicine, New York City, 1909; served as secretary of the Bronx Medical Society; associated with the Physicians Hospital in Jackson Heights, Medical Arts and Manhattan General hospitals; died June 12, aged 75.

Meyer, William Henry, Chicago; Medical College of Ohio, Cincinnati, 1898; honorary staff member at the Grant Hospital, where he died June 8, aged 88.

Miller, George Brady, Cleburne, Texas; Chattanooga (Tenn.) Medical College, 1907; veteran of World War I; died June 3, aged 77.

Moore, Paul Herman ⊛ Los Angeles; Western Reserve University School of Medicine, Cleveland, 1918; associated with the Holly Presbyterian Hospital, where he was past-president of the staff, and where he died June 8, aged 68.

Nichols, Virgil Newton, Carson, Miss.; Memphis (Tenn.) Hospital Medical College, 1904; died June 6, aged 82.

O'Donnell, Joseph Martin ⊛ Hollister, Calif.; Medical Department of the University of California, San Francisco, 1902; for 34 years president of the San Benito County High School and Junior College board of trustees; served as director of the Hollister Branch of the Bank of America; died May 25, aged 81.

Pace, George Delmont, Saugerties, N. Y.; Long Island College Hospital, Brooklyn, 1908; served in France during World War I; associated with Benedictine Hospital in Kingston for many years; died May 20, aged 73.

Plumley, William Franklin ⊛ St. Petersburg, Fla.; University and Bellevue Hospital Medical College, New York City, 1902; veteran of World War I; for many years practiced in Rochester, N. Y., where he was associated with the Rochester General Hospital; died in Mound Park Hospital May 24, aged 81.

Powe, Walker Halliburton ⊛ Greenville, S. C.; Medical College of South Carolina, Charleston, 1911; past-president of the Greenville County Medical Society; member of the American Academy of General Practice; veteran of World War I; member of the city council; for many years member of the city board of health; associated with St. Francis and Greenville General hospitals; died May 24, aged 72.

Rench, Victor Bell, Washington, D. C.; Columbian University Medical Department, Washington, 1895; served on the staff of the Episcopal Eye, Ear and Throat Hospital; died in the Washington Sanitarium and Hospital, Takoma Park, Md., June 5, aged 88.

Rickman, Samuel Moir ⊗ Paris, Ky.; Emory University School of Medicine, Atlanta, 1930; member of the Southeastern Surgical Congress; served in the Pacific theater during World War II; past-president of the Bourbon County Medical Society; on the staff of the Bourbon County Hospital; died May 21, aged 56.

Robertson, William Sterling ⊗ Charleston, W. Va.; University College of Medicine, Richmond, 1905; member of the American Urological Association; died June 13, aged 78.

Romano, John Rock ⊗ Chicago; Loyola University School of Medicine, Chicago, 1919; veteran of World War I; member of the pension rating board of the Veterans Administration for many years; associated with Mother Cabrini, St. Bernard, and the Veterans Administration West Side hospitals; died in St. Anne's Hospital June 12, aged 70.

Rowntree, Leonard George ⊗ Miami, Fla., formerly chief of the department of medicine of the Mayo Foundation and head of a section of medicine in the Mayo Clinic in Rochester, Minn., died at Jackson Memorial Hospital, June 2, aged 76. Dr. Rowntree was born in London, Ont., April 10, 1883. Following his graduation from the University of Western Ontario Faculty of Medicine in London, Ont., in 1905, he interned at the Victoria Hospital in London, Ont. In 1906 he came to the United States to establish a practice in Camden, N. J., and the following year he joined the faculty of Johns Hopkins University School of Medicine in Baltimore as a voluntary assistant in pharmacology and experimental therapeutics and subsequently became assistant instructor, associate, and associate professor, serving in these various capacities until 1914, when he became associate professor of medicine. From 1916 to 1920, Dr. Rowntree was professor of medicine and chief of the department of the University of Minnesota Medical School in Minneapolis and from 1920 to 1932 was professor of medicine and chief of the division of medicine at the Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn., and senior medical consultant and director of clinical research at the Mayo Clinic. From 1932 to 1946 he was director of the Philadelphia Institute for Medical Research and research clinician at the Philadelphia General Hospital. In 1938 he received the annual Strittmatter Award, a gold medal, of the Philadelphia County Medical Society for his work on the thymus gland, cancer, and arthritis. In 1944 he was awarded the Banting Memorial Medal by the American Diabetes Association for serving as a Banting lecturer. Dr. Rowntree was chairman of the deans' committee of the Veterans Administration Hospital in Coral Gables, Fla., from 1946 to 1955 and member of the advisory board of the Biochemical Research Foundation in Newark, Del., from 1933 to 1955. During World War I he was a major and then a lieutenant colonel in the medical corps of the U. S. Army, and was executive officer of the medical research laboratories of the Air Service of the American Expeditionary Forces. Later he was the American representative at the first Congress on Aviation Medicine, held in Rome. He served as chief of the medical division of the headquarters office of the Selective Service System in Washington, D. C., from 1940 to 1945. In 1945 was the recipient of the Medal of Merit from President Harry S. Truman. In 1944-1955 he was chairman of the National Joint Committee on Physical Fitness of the Federal Security Administration and from 1945 to 1950 chief medical advisor and chairman of the medical advisory board of the American Legion. In 1944 received a scroll of honor by the New York State Committee on Physical Fitness. He assisted in the founding of the University of Miami School of Medicine. A specialist certified by the American Board of Internal Medicine, Dr. Rowntree was past-president of the American Society for Clinical Investigation and the American Society of Endocrinologists. He was a fellow of the American College of Physicians, a member of the Association of American Physicians, American Association for the Advancement of Science, American Physiological Society, American Association for the Study of Internal Secretions, American Pharmacological Society, American Society of Biological Chemists, American Society for Experimental Pathology, the Alumni Association of the Mayo Foundation, Phi Beta Kappa, the Society of the Sigma Xi and the Phi Beta Pi professional medical fraternity. He served as vice-president of the National Committee on Mental Hygiene. Dr. Rowntree was chairman of the Section on Pharmacology and Therapeutics of the American Medical Association in 1920-1921, member of its House of Delegates in 1922-1923, and from 1916 to 1936 was a member of the Council on Pharmacy and Chemistry. He devised and introduced the phenosulphonphthalein test for the diagnosis of disease of the kidney, and was a pioneer in demonstrating water intoxication of the body, the beneficial effect of cortin in Addison's disease, and the role of the thymus and pineal glands in growth and development; identified an agent in wheat-germ oil made by ether extraction which would cause a form of cancer in rats. In 1958 the story of his life and career, "Amid Masters of Twentieth Century Medicine: A Panorama of Persons and Pictures," was published. In 1916 he was awarded the honorary degree of doctor of science by the Western University of Ontario, and in 1958 received the honorary degree of doctor of letters from the University of Miami.

Rubin, David, Cleveland; Western Reserve University School of Medicine, Cleveland, 1953; American Cancer Society fellow in medicine at the University Hospitals, where he served an internship and residency; died June 2, aged 33.

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Santillo, Giovanni ⊗ Staten Island, N. Y.; Regia Università degli Studi di Roma. Facoltà di Medicina e Chirurgia, Italy, 1923; associated with St. Vincent's and Staten Island hospitals; died June 15, aged 62.

Schmid, Henry John ⊗ Harvard, Ill.; Bennett Medical College, Chicago, 1909; chairman of the board of health; past-president of the Harvard Chamber of Commerce and the Harvard Rotary Club; associated with the Harvard Community Memorial Hospital, where he died June 8, aged 83.

Schneider, Elwin Carl ⊗ Alexandria, Va.; Georgetown University School of Medicine, Washington, D. C., 1905; died June 11, aged 79.

Shacklette, Warner J. ⊗ Hodgenville, Ky.; Hospital College of Medicine, Louisville, 1898; honorary staff member of the Glasgow (Ky.) Community Hospital, where he died June 7, aged 88.

Shields, Harold Franklin ⊗ Chickamauga, Ga.; Atlanta College of Physicians and Surgeons, 1908; on the staff of the Hutchison Memorial Hospital in Fort Oglethorpe, where he died May 7, aged 78.

Skinner, William Frederic ⊗ Easton, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1931; interned at the George F. Geisinger Memorial Hospital in Danville; veteran of World War II; fellow of the Industrial Medical Association; served as vice-president of the Pennsylvania Heart Association; past-president of the Lehigh Valley Heart Association; plant physician for the Riegel Paper Corporation in Milford, N. J., and medical consultant for Ingersoll-Rand Company; on the staffs of the Betts Hospital and the Warren Hospital, where he died June 5, aged 55.

Smelser, Herman Wayne ⊗ Connersville, Ind.; Indiana University School of Medicine, Indianapolis, 1916; for many years member of the public school board; a veteran of World War I; in 1935 was made health officer of Connersville and Fayette County; member of the board of the Fayette Memorial Hospital; died May 29, aged 67.

Snow, John Wesley Jr. ⊗ Graysville, Ala.; Medical Department of Grant University, Chattanooga, Tenn., 1907; died May 25, aged 78.

Staats, Phillip Thomas ⊗ Portland, Ore.; University of Oregon Medical School, Portland, 1936; member of the American Academy of General Practice; served on the staff of the Holladay Park Hospital; died May 11, aged 49.

Stauffer, Nathan Pennypacker ⊗ Philadelphia; Jefferson Medical College of Philadelphia, 1901; also a dentist; fellow of the American College of Surgeons; from 1896 to 1899 professor of hygiene at the Dickinson College in Carlisle, Pa., and the University of Mississippi in University from 1906 to 1912; served on the staffs of the Delaware County Hospital in Drexel Hill, Pa., Girard College, and Presbyterian Hospital; died June 5, aged 84.

Swetnam, Elmer, Lexington, Ky.; Kentucky School of Medicine, Louisville, 1903; died March 7, aged 81.

Tabler, Homer E. ⊗ Hancock, Md.; Maryland Medical College, Baltimore, 1904; at one time chairman of the State Roads Commission; member of the American Academy of General Practice; died June 9, aged 78.

Thompson, Clarence Philip ⊗ San Francisco; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1907; member of the American Academy of General Practice; president emeritus of the board of trustees of St. Francis Memorial Hospital, where he was board president for 20 years, and where he died June 9, aged 73.

Thompson, Will Ambrose ⊗ Liberty, Ind.; Indiana University School of Medicine, Indianapolis, 1909; served as vice-president of the Indiana State Board of Medical Registration and Examination; past-president of the Wayne-Union Counties Medical Society; county health officer; died in the Reid Memorial Hospital, Richmond, June 5, aged 81.

Veigel, Lester Paul ⊗ Colonel, U. S. Air Force, Hamilton Air Force Base, Calif.; born in Dickinson, N. D., March 16, 1905; Northwestern University Medical School, Chicago, 1931; appointed to first lieutenant in the Army of the United States Nov. 4, 1932, and reported for active duty Dec. 10, 1932; commissioned a first lieutenant in the U. S. Army on July 1, 1933; transferred to the U. S. Air Force on July 22, 1949; from 1950 to 1954 a staff officer in the Office of the Surgeon General and from 1954 to 1957 commander of the hospital at Orlando Air Force Base, Fla.; chief surgeon of the Western Air Defense Force; during World War II was awarded the Bronze Star while serving in the European Theater of Operations; member of the Aero Medical Association; specialist certified by the American Board of Preventive Medicine; died June 3, aged 54.

Watman, Morris ⊗ Miami Beach, Fla.; Long Island College of Medicine, Brooklyn, 1930; veteran of World War II; retired from the Veterans Administration Dec. 31, 1956; associated with the Veterans Administration Hospital and regional office in Waco, Texas, for many years; died in New York City May 31, aged 53, while on a vacation trip.

Williams, John Nelson, Pound Ridge, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1903; died June 5, aged 83.

Young, L. Randle, Indianapolis; Indiana University School of Medicine, Indianapolis, 1934; died May 28, aged 50.

FOREIGN LETTERS

AUSTRIA

Stenosis of Bile Duct.—At the meeting of the Society of Physicians in Vienna, on April 17, P. Fuchsig reported a series of three patients who had been operated on unsuccessfully several times elsewhere for postoperative stenosis of bile ducts and whom he treated by hepaticoenterostomy. The common hepatic artery serves as a guiding structure. A transhepatic cholangiogram clarifies the position of the confluence of both the intrahepatic branches of the hepatic duct at the start of the operation. The method goes a step further than the "pointed plastic" operation of Gotze but avoids the still more radical "intrahepatic cholangioenterostomy" of Dogliotti and Longmire. One of the patients was free of symptoms for a long time after operation but brief attacks of cholangitis always recurred after dental extractions. This raised the question of a focal origin of these bouts, but no satisfactory answer was found.

Cervical Venous Pressure and Thyroidectomy.—At the same meeting K. Keminger and N. Maager reported that they determined the pressure in the superficial and deep cervical veins of 45 patients and 15 rabbits. The effect of high-pressure respiration and of the patient's position was studied during thyroidectomy. It was established that venous air embolism could not be prevented by intubation anesthesia or low positioning of the head alone. Entrance of air could be prevented only during the phase of forced high pressure. An effective rise in venous pressure can be maintained for two minutes, at most, since it is accompanied by a rapid drop in pressure of the arterial system. These observations were confirmed by the production of air embolism in animal experiments. Each change in the venous pressure favored the occurrence of air embolism, but this risk may be combatted by intubation in combination with the use of long-acting muscle relaxants.

Fuchsig stated that intubation anesthesia reduces the risk of air embolism associated with thyroidectomy. In the surgical department of the Empress Elizabeth Hospital six cases of air embolism were observed in 16,900 thyroidectomies and one fatal case of air embolism was observed in an additional 3,300 thyroidectomies. These occurred only in patients who had not undergone intubation. On the other hand K. Huber from the first surgical University Clinic in Vienna described two deaths from air embolism which occurred in patients in the recumbent position during intubation anesthesia. The speaker believed that high-pressure respiration could reduce the risk of pulmonary embolism, but only within certain limits and provided that it is performed properly. By thus eliminating irregularities in breathing and bouts of coughing, intubation anesthesia for thyroidectomy is superior to all other methods of anesthesia.

Osteomyelosclerosis.—At the same meeting R. Klima stated that osteomyelosclerosis with progressive fibrosis and narrowing of the marrow space by new bone formation leads to an elimination of blood formation in the marrow, with activation of a compensatory hematopoiesis in the spleen and liver, which can balance the decrease in marrow function at least partially and occasionally for a prolonged period. The substitute formation of blood, however, is inconstant and frequently pathological. Particularly in the late stages progressive anemia and thrombopenia occur frequently. Occasionally there may also be excessive cell production, which leads to leukemoid conditions with enlargement of the spleen and liver, and thus erythroblasts and megakaryocytes may be carried into the blood.

The diagnosis is suggested in case of empty sternal puncture by the recognition of immature myeloid and erythroblastic cells as well as megakaryocytes in the blood, by the establishment of extramedullary blood formation with the aid of liver biopsy, and by bone biopsy, if x-ray findings in the skeleton are negative. With the use of these methods 59 cases were discovered in six years. The cause is not clear. Radiation therapy or chemotherapy might play a part in patients with secondary osteomyelosclerosis, such as occurs in the course of chronic myeloid leukemia and after polycythemia respectively.

H. Rieder stated that osteomyelosclerosis is characterized by (1) progressive fibrosis and sclerosis of the bone marrow; (2) a high degree of splenohepatomegaly due to the occurrence of a compensatory extraosseous formation of blood; and (3) a myeloid-erythroblastic blood picture. The substitute hematopoiesis at the onset is sufficient or excessive (polycythemic early stage), but later becomes progressively deficient so that severe anemia, which finally causes the patient's death, results. The leukocyte count is usually high but, as a rule, not over 50,000 per cubic millimeter. Leukopenia occasionally occurs. Although thrombocytosis with more than 1,000,000 platelets per cubic millimeter

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occurs rarely, thrombopenia occurs much oftener. Occasionally there may be hemorrhagic diathesis and, rarely, hemolysis.

The diagnosis is made from empty marrow or from marrow poor in cells, the enlargement of the spleen, and the myeloid-erythroblastic blood picture. The occurrence of megakaryocytes in the peripheral blood, determined best in the leukocyte concentration, is characteristic. With the systematic use of the methods mentioned the differential diagnosis from subleukemic myelosis, polycythemia vera, panmyelophthisis, and hepatosplenomegaly of other origin does not usually offer any difficulties. The disease most frequently occurs after the 40th year and in general has a more benign course than chronic leukemia. Therapy consists of repeated blood transfusions and symptomatic measures.

H. Cztober reported that bone biopsy is a relatively simple clinical method of investigation and is free of risk. It provides for a direct observation of changes in structure, not only of the bone tissue but also of the marrow. The microscopic findings offer valuable diagnostic possibilities for the differentiation of diseases of the blood and other diseases of marrow. This method makes it possible for the first time to study the disease processes in the marrow during life. The course of the disease is characterized by osteoclasis, progressive fibrosis of the marrow, and subsequent active new formation of bone.

G. Hartmann stated that the pathological changes in the marrow typical of osteomyelosclerosis consist of an increasing fibrous obliteration of the marrow, which begin multicentrically with disturbances of blood perfusion, plasma diapedesis, and small foci of necrosis, which produce a myelofibrosis either immediately and gradually or by way of a variegated granulation tissue of the marrow mesenchyma. In late stages an endosteal hyperostosis is typical. The vicarious secondary hemocytopoiesis in spleen and liver leads to the characteristic hepatosplenomegaly. The histological findings in the marrow correspond rather to the graded course of a degenerative inflammatory process and do not favor the consideration of a neoplastic (leukocytic or reticulocytic) process. The cause is unknown and probably varies from case to case. Osteomyelosclerosis, therefore, may be considered as a well-defined clinical and pathological syndrome.

R. Formanek reported that in 50 patients with confirmed osteomyelosclerosis who were subjected to roentgenologic examinations, partly diffuse and partly focal hardening of the spongy substance of moderate to severe degree was observed in the area of the skeleton of the trunk and of the proximal portions of the extremities. Eleven patients showed multiple porotic and osteolytic foci, respectively, in addition to focal hardening. It is difficult for the roentgenologist to differentiate between these pathological changes and those of generalized and mixed osteoplastic metastases. Cooperation with the clinician is indispensable to clarify the diagnosis. Differentiation between osteopetrosis (Albers-Schönberg disease) and osteomyelosclerosis can be made by the occurrence of osteopetrosis during the age of growth, enlargement of metaphyses, and band-like hardening of the long, tubular bones. Spontaneous fractures were not observed.

BRAZIL

Retroperitoneal Tumors.—F. Paulino and co-workers of the Rio de Janeiro Hospital São Miguel (*Revista brasil.* 37:103, 1959) studied a series of 18 patients who had primary retroperitoneal tumors. Patients with metastatic growths or primary tumors of the kidneys, adrenals, and pancreas were not included. The authors defined the retroperitoneal region as the poorly demarcated space at the lumboiliac level between the parietal peritoneum in front and the muscular mass of the region in the back, containing fat, vessels, nerves, lymph nodes, kidneys, ureters, and the posterior faces of the duodenum and pancreas. The abundance of lymph nodes explains the high incidence of metastatic or secondary tumors. The 18 patients were distributed between the age group under 9 years (3 patients) and the age group 70 to 79 years (1 patient). In 5 patients the tumors were benign (two lymphangiomas, two retroperitoneal cysts, and one teratoma) and in the other 13 the tumors were malignant (9 lymphosarcomas, two reticulosarcomas, one lipomyxosarcoma, and one ganglioneuroblastoma).

All the lymphosarcomas and the two reticulosarcomas formed voluminous polycyclic masses on both sides of the vertebral column, invading the mesentery and in some cases the peritoneal cavity. The lipomyxosarcoma formed an encapsulated tumor of a firm consistency. It was resected by dissection around its capsule because the surgeon thought it benign, but it reappeared in the same site and was operated on again one year later by radical dissection of the perirenal fat and nephrectomy. When the patient was seen two years later he had no evidence of relapse. The ganglioneuroblastoma of the lumbar sympathetic chain was adherent to the iliac vessels and the ureter. It was incompletely resected because of the direct invasion of the iliac vessels. In spite of postoperative roentgenotherapy a relapse occurred about a year after operation.

The more frequent symptoms of the neoplasms were abdominal pain, loss of weight, and palpable tumor. Two patients sought medical care because of enlargement of the abdomen. In one of the patients with lymphosarcoma, examined in the terminal stage, there were jaundice, hematemesis, and melena.

The simple x-ray examination of the abdomen was useful for the initial location of the tumor mass, the examination being completed by the use of a con-

trast medium to ascertain the posterior limits of the tumor and demonstrate compressions and deviation of digestive organs. Venous pyelography was indispensable and in some patients artificial perirenal emphysema was useful. Hemograms and marrow and lymph node biopsy also aid in establishing the diagnosis. Resection of benign tumors gave excellent results. Even large tumors which cause compression of adjacent organs, including the aorta and the vena cava, can be removed, provided careful dissection is performed.

Action of Radium on Poliovirus.—J. G. Lacorte and co-workers of the Rio de Janeiro Oswaldo Cruz Institute (*Revista brasil. med.* 16:247, 1959) studied the behavior of poliovirus under irradiation. These authors had previously shown that weak doses of x-rays caused an increase of the pathogenicity of the influenza virus.

The present experiments were performed with a strain of type 2 poliovirus called MEF1. Animals were inoculated by injections of 0.03 cc. of a suspension of the virus intracerebrally. The initial dilution was divided in two portions, one of them subjected to the action of four tubes of 1 mg. of radium each. The titrations made after 60 and 90 days of exposure showed an increased activity of the virus subjected to the action of radium. After 127 and 159 days the nonirradiated control virus had lost all its activity, while that of the irradiated virus was unchanged.

Cytomegalic Inclusions in Children.—The geographical distribution and incidence of cytomegalic inclusions varies widely. In Brazil the first cases were described only a few years ago, and recently A. P. Garcia, of the Rio de Janeiro Hospital Fernandes Figueira (*Hospital* 55:23, 1959), reported two cases in newborn babies and two in infants, from a series of 150 successive autopsies of children. Diagnosis was not made by previous clinical suspicion nor was the gross examination, at autopsy, sufficiently decisive. It was therefore necessary to examine the salivary glands microscopically, a procedure that is now performed routinely. One of the newborn babies was premature, with icterus, purpura, splenomegaly, and hepatomegaly. The other had an infection with pallor, omphalitis, peritonitis, and visceral hemorrhages.

The two infants showed severe undernourishment, with predominant respiratory symptoms in one and gastrointestinal symptoms in the other. Both had interstitial pneumonia and one of them had ulcerative enteritis, in the exudate of which Monilia was found. Typical cytomegalic elements were identified in several organs, more frequently in kidneys and lungs, and much more numerous in the newborn infants who had septicemia. Lesions of the nervous system were found in all four patients, under the form of meningoencephalitis. The parenchymatous lesions were mainly situated on the walls of the lateral ventricles (hyperplasia of the ependymal cells and of the subependymal glia, depositions of calcium and iron, and perivascular round cell infiltration). In one of the newborn infants the infection became extremely severe and produced necrosis of a great part of the right hemisphere, followed by numerous foci of calcification. In the other the lesions were essentially hemorrhagic. In both infants there were leptomeningitis and ependymitis, producing zones of ulegyria and ventricular dilatation.

CANADA

Needle Aspiration Diagnosis of Solid Tumors.—For about 20 years the Ontario Cancer Foundation's Clinic in London, Ontario, has studied the diagnostic value of histological interpretation of tumor aspirates. In the last few years persons working in this clinic have realized that the cytological interpretation of tumor aspirates is a most valuable procedure, and it has replaced study of sections in some instances. In diagnosis of primary malignant tumors of lymph nodes, however, it is still inferior to the study of sections. Smith and co-workers (*Canad. M. A. J.* 80:855, 1959) studied aspiration cytology in 203 cases of cancer and 194 cases of deep-seated benign disease. They used a 22-gauge needle to withdraw tissue fluid which was smeared on egg albuminized slides, fixed while still wet, and stained by hematoxylin-eosin. By this method 93% of cases of mammary cancer were confirmed cytologically, though in 18% more than one aspiration was needed. Preoperative diagnosis by this method permitted a planned therapeutic approach and eliminated the need for frozen section studies. Aspiration cytology also confirmed 94% of diagnoses in secondary metastases in lymph nodes. In the study of 194 benign cases (cystic disease and fibroadenoma of breast, lymphadenitis, benign thyroid disease, etc.) there were only 5 false-positive findings, whereas in the 203 cases of malignant disease there were 18 (or 8.8%) false-negative results. Smith believes that, because of its simplicity, accuracy, and practical value, aspiration smear cytology for solid tumors deserves wider application.

Sudden Death in Infants.—Sudden and unexpected death in infants has been attributed to asphyxia and infections without definite confirmation. Handforth of Halifax, Nova Scotia (*Canad. M. A. J.* 80:872, 1959) has another suggestion based on his careful study of autopsy material from 12 infants who died suddenly while apparently healthy, and some experiments on anesthetized rats. The lesions found in the infants were comparable to those produced by acute asphyxia in the rats. There

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were petechiae in the lungs, heart, and thymus. A pink frothy fluid was expressed from the congested lungs. No cause of respiratory obstruction could be found. Microscopically, inflammatory cells were found in only two cases, and no pathogen was isolated from the heart or lung blood. The rat experiments showed that temporary respiratory obstruction could produce fatal apnea, and the author, dissatisfied with the infection theory, suggests that these infants died of laryngospasm, possibly associated with a mild upper respiratory infection.

Influenza Vaccine.—In a mental hospital in Alberta, 1,035 long-term patients participated in a study of Asian influenza vaccine. Each was given a subcutaneous injection of 1 cc. of either vaccine or placebo. Observations were maintained for 17 weeks from October to January, during which time an epidemic among the general population reached its peak. Of the 519 patients given vaccine, clinical symptoms of influenza were recorded in 30, or 5.8%, while among the 516 given placebo symptoms were observed in 75 or 14.5%. Only two patients died from pneumonia, one in the placebo group and one in the vaccinated group. This suggested a protection rate of 60% from the vaccine. An interesting sidelight on the trial was the result of inoculating 349 staff members of this institute with Asian influenza vaccine about a week after inoculating the patients. In this group there was a 42% incidence of clinical symptoms of influenza, i. e., nearly three times the incidence observed among unvaccinated patients. It is clear that comparison between patients and staff is not valid in these circumstances.

Voluntary Medical Insurance.—The Department of National Health and Welfare, Ottawa, prepared a brochure on voluntary medical insurance with reference to 1957 experience. The statistics analyzed refer to medical care insurance only and not to hospital insurance. By the end of 1957, about 7,800,000 persons or 47% of the total Canadian population had purchased some type of voluntary medical insurance and an additional 300,000 persons were covered by publicly sponsored medical care programs in certain areas of Manitoba and Saskatchewan. Of the total voluntarily insured, 4,100,000 persons had purchased physicians' service contracts offered by nonprofit agencies while 3,700,000 were policy holders of private insurance companies. These totals represented a 14% increase in membership for the former type and an 8% increase in the latter in 1957. The total benefit payments on medical insurance claims in Canada rose to nearly 90 million dollars in 1957, of which about 71% was expended by nonprofit plans on behalf of their subscribers. This 90 million dollars represented about 46% of all professional payments made to civilian physicians in private practice in Canada that year.

The statistical analysis reveals certain significant developments in voluntary health insurance in 1957 and 1958. Major medical contracts, including hospital, medical, and surgical coverage, designed to take care of the large financial demands of catastrophic illness, have become increasingly popular. This is true for nonprofit plans and also private insurance companies. The authors also point to the formulation by the Canadian Dental Association of a new type of plan for "post-payment" of dental expenses on a monthly basis, and the appearance of a nonprofit company entitled Canadian Optometric Services, Inc., which will provide full optometric services on a prepayment basis.

Adolescents in a Mental Hospital.—In the provincial mental hospital in British Columbia, adolescent patients with both psychotic and nonpsychotic diagnoses caused trouble out of all proportion to their numbers. Since it was impossible to segregate them in wards for teen-agers, an attempt was made by group therapy to improve the situation. Powles (*Canad. Psychiat. A. J.* 4:77, 1959) reported the results of a three and one-half year pilot project in group treatment of these emotionally ill adolescents. Meetings were held twice or three times a week in which group psychotherapeutic techniques were combined with social group work, requiring a total staff effort of about 25 man-hours weekly. The group included patients of both sexes ranging in age from 14 to 24 years and with diagnoses of neurotic, psychotic, and behavior disorders. In the latter part of the period about half the members were given individual somatic and psychological treatment, but in the first half of the existence of the group, the group therapy was the only specific therapy most of the members received. Powles suggested that perhaps the single greatest benefit from group therapy was the development of a consciousness among staff members, in general, that this age group could be assimilated and dealt with in treatment. Within a year of the inception of group therapy grossly disturbed teen-agers became a rare problem in the hospital. In view of the poor results obtained with the psychotic members of the group, it is questionable whether they should be included in such groups. On the other hand, persons with quite severe behavior disorders improved surprisingly. Taking the group as a whole, there were 17 good, 23 fair, and 16 poor results.

GERMANY

Late Results in Treatment of Tuberculosis.—W. Schaich of the tuberculosis sanitarium in south Baden reported (*Tuberk.-Arzt.* 13:176, 1959) a

series of 173 tuberculosis patients who in the years 1947 to 1950 were treated with at least 14 Gm. of streptomycin, 400 Gm. of para-aminosalicylic acid (PAS), and 10 Gm. of amithiozone for at least eight weeks. A follow-up study revealed that 149 patients (86.14%) were still living. Of the entire series 61 had received only chemotherapy and 112 had also had pulmonary collapse. Of the 52 surviving patients in the group treated with chemotherapy alone 32 had had open cases at the start of treatment and 7 had open cases at the time of the study. Of the same 52 only 33 were able to work. Of the 97 survivors in the group treated with chemotherapy plus collapse 89 had had open cases at the beginning of treatment and 26 had open cases at the time of study. Of the 97 only 46 were able to work. Of a total of 121 infective patients (with open cases) the tuberculous processes had closed in 88, or 72.7%. In comparison with the results obtained prior the chemotherapeutic era with conservative and collapse treatment, the present results are excellent.

Contagion in Tuberculosis.—Forsbach and Klover (*Tuberk.-Arzt.* 13:27, 1959) observed a series of 505 tuberculous patients with first infections (425 in children 1 to 14 years of age and 80 in adolescents 15 to 21 years of age). The source of infection was found to be intradomiciliary in 45%, extradomiciliary in 10.6%, and in 44.4% was undetermined. Intradomiciliary infection was most frequent among the 1-to-3-year-old patients (52.5%). Eleven patients who had earlier been immunized with BCG vaccine had a mild course of the disease. Intrapulmonary foci were found in only one patient, who had been so vaccinated at 5 years of age. Six years later he was tuberculin-negative and did not have clinical tuberculosis until nine years after vaccination. Tubercle bacilli from gastric washings—rarely from sputum cultures or laryngeal smears—were recovered in 27.5% of the children and 33.8% of the adolescents with primary tuberculosis. In cases of primary tuberculosis the patients' contacts should be examined. Tuberculosis should also be considered an occupational hazard in nursing personnel attending children.

SWEDEN

Ketogan in Midwifery.—At the Maternity Department of the Sahlgrenska Hospital in Gothenburg, Dr. H. Crona (*Svenska läkartidningen*, April 30, 1959) tested Ketogan for its analgesic effect on the expulsive stage of labor. His series of 122 patients, mostly primiparas, had severe pain during the expulsive stage and were restless and nervous. They showed no signs of toxemia, heart disease, jaundice, or threatened complication. Each of the 1-cc. ampuls used was numbered, to distinguish between those containing the drug and those containing a placebo. Each patient received the contents of only one ampul. Of the 62 patients given Ketogan 36 obtained relief, whereas of the 60 who received the placebo only 2 were relieved. In the Ketogan-treated group 55 achieved some degree of analgesia, whereas in the control group there were 11 such patients. The drug provoked no asphyxia or other undesirable side-effect, nor did it seem to prolong the duration of labor.

Bedside Diagnosis of Heart Disease.—Akesson and Bagger sought to find out how much can be learned about candidates for cardiac operations by the comparatively simple methods of inspection, palpation, percussion, auscultation, and blood-pressure measurements in the absence of a case history (*Nordisk medicin*, May 7, 1959). Their series of 128 patients included 71 with mitral disease and 16 with combined mitral and aortic valvular disease. They found that uncomplicated acquired mitral stenosis could be diagnosed with almost 100% certainty by bedside methods alone, but a combination of mitral with aortic valve disease presented diagnostic pitfalls dangerous for the clinician who relies on bedside methods only. Even frank mitral stenosis is likely to be overlooked by them. In the light of the findings of more modern tests applied to these patients, the bedside tests do, however, emerge from the comparison creditably, within the above-indicated limits.

Late Effects of Traffic Accidents.—G. Hellström (*Svenska läkartidningen*, May 15, 1959) made a follow-up study five years after their discharge from hospital of the conditions of 396 patients who had had traffic accidents. He reexamined 115 of the most seriously injured and found that in 63 recovery was incomplete. Of the 60 who had suffered from concussion and had been kept in hospital for over seven days 32 still had some discomfort. Of the 55 whose injuries to other parts of the body had entailed a stay in hospital of over four weeks 31 still suffered from the effects of the accident, although most of them had been able to resume their former occupations. Less measurable but probably frequent must have been the emotional conflicts precipitated by concussion of the brain from a traffic accident.

Primary Hyperparathyroidism.—That hyperparathyroidism is not rare was shown by J. Hellström (*Nordisk medicin*, April 9, 1959), who observed 115 cases. The fact that 93 of them dated from 1950 suggested that the diagnosis of this disease hinged largely on the interest taken in it. Fully 70% were women, and the age of the patients ranged from 16 to 71 years. There had been symptoms of the disease for an average of eight years before it was recognized. Roentgenologically demonstrable changes in the kidneys, in the form of stones or

nephrocalcinosis, were found in 85%. Even in the absence of roentgenographic changes the kidneys were always involved, being at first the subject of functional and transient disturbances. The only rational treatment is operative removal of the glands, for medicinal and radiologic treatment have proved futile. The prognosis depended largely on the degree of damage to the kidneys before the parathyroids were removed. Without any treatment the prognosis was poor, although in some patients the disease might last for decades.

Malformed Offspring of Older Mothers.—To find statistical proof of the teaching that the offspring of mothers aged over 42 are more likely to have congenital abnormalities than others Lindsten and Hagert (*Nordisk medicin*, May 14, 1959) counted such abnormalities in the offspring of 1,030 mothers over 42 years of age confined at three teaching hospitals during the period 1946-1955. Serving as controls were the cases collected by J. A. Böök, who in 1951 reported his study of congenital malformations occurring in the offspring of mothers of various ages. While the rate of congenital malformation for the offspring of older mothers was 45.1 per 1,000 births, the corresponding rate for the controls was only 13.4. For Mongolism, of which there were 22 cases in this study, the rates were 21.1 and 0.45 respectively. For hydrocephalus they were 1.9 and 0.54 respectively.

Medical Costs.—The government increased the cost of doctors' house calls. In Stockholm, the fee went from $3 to $3.60 and in the rest of the country from $2.30 to $2.90. For insured persons the cost of reimbursed medical services is the same for consulting room or house call. Total cost of insurance has been estimated at $450,000 to $490,000 yearly; about half is borne by the state. The basic rate for x-ray examination went up by about $2. The difference in rates between the first and subsequent consultations was abolished. Hospital insurance, despite increased premiums, had 621,515 members in January, 1959, compared with 615,524 in October, 1958, or 77.2% of Stockholm's population compared with 77.0% in October.

Cardiac Catheter in Patients with Burns.—In the fourth paper of a series of studies on burns, G. Birke and co-workers (*Acta chir. scandinav.* 116:362-369, 1958/1959) advocated prolonged use of an indwelling catheter in the pulmonary artery for studies of circulation and for intravenous infusion. Patients with extensive burns are, during the acute phase, wholly dependent on intravenous replacement therapy. Since these patients are often restless and thus likely to displace inserted drip cannulas, and since many of them have no easily accessible veins, the technique of administration presents a great problem. Insertion of a cardiac catheter has been found to be a safe method for intravenous infusion of fluid. The report covered a series of eight patients with severe burns who had a cardiac catheter in the pulmonary artery for 1½ to 11 days.

An autopsy was performed on five of the patients who died. No lesions in the endocardium, myocardium, tricuspid valve, or pulmonary valve were seen. In two of them a thickening of the intima, 1 by 2 cm. in size, was seen in the right main branch of the pulmonary artery in one case, and in the left main branch in the other, corresponding to the position of the tip of the catheter. In the rest in whom the tip of the catheter was placed in the right main branch the arterial wall was wholly intact. Microscopic examination in the two first mentioned showed disintegration of the vascular intima with splitting of the elastic fibrils and a few leukocytes. On the injured vessel wall there was a thrombotic deposit consisting mainly of fibrin but also containing red blood cells. In three patients there were mural thrombi in the peripheral brachial vein. No pulmonary emboli were seen in any of the patients. In the three surviving patients who had the catheter for two to three days no complications were seen. The arterial catheter which was left for the same period of time as the heart catheter did not cause any complications.

Since prolonged use of a cardiac catheter in the pulmonary artery has not caused any severe injuries or any discomfort to the patients, this method can be recommended in the management of severe burns, particularly because it facilitates collection of valuable information concerning the central circulation. For fluid therapy it may be sufficient to place the tip of the catheter in the superior vena cava or in the right auricle. Placing it in the pulmonary artery, however, enables one to make measurements which are of greater value in the assessment of the circulation of the blood, and this position is therefore to be preferred in these patients, if it is technically possible. The risk of thrombosis in the peripheral vein is probably equal with the tip of the catheter in the pulmonary artery or in the vena cava. Several of the catheterized patients showed signs of systemic infections like those generally observed in patients with extensive burns. There was no evidence in these patients suggesting that the cardiac catheter had given rise to, or maintained, infections, nor were any septic emboli seen in the lungs.

Circulation and Respiration in Burned Patients.—In the fifth paper in a series of studies on burns G. Birke and co-workers (*Acta chir. scandinav.* 116:370-394, 1958/1959) stated that shock, or threatened shock, is a major problem in the treatment of extensive burns. In the first four to eight hours after injury a reduced blood volume is combined with a lowered blood pressure in the right auricle, reduced cardiac output, usually a normal arterial blood

pressure, and increased peripheral vascular resistance. At the same time there is an increased oxygen consumption. The reduced blood volume in the central vessels and the lungs with a deficient filling of the left ventricle is probably of fundamental importance to the disturbed hemodynamics. After transfusions both the cardiac output and the peripheral vascular resistance become normal.

In the series of eight patients referred to in the fourth paper the circulation and respiration were studied. Initially, in spite of the usual fluid therapy, there were signs of hypovolemic shock with small stroke volume and cardiac output, but often ordinary arterial blood pressure, raised pulse rate, high peripheral vascular resistance, low or normal pressure in the pulmonary artery, and high secretion of epinephrine, arterenol, and corticosteroids were present. Together these observations indicate the necessity of ample administration of colloids, preferably whole blood. During the so-called absorption phase, from the third to the sixth day, slightly increased blood volumes were seen in six patients, but in spite of this most patients seemed to have had an insufficient central blood volume. These results indicated that in most patients there was reason to give larger amounts of colloids during this phase than had generally been used. In the first 48 hours after the burn and later a distinction was made between patients in whom hypovolemia and those in whom myocardial insufficiency predominated.

Patients in the first group had a small stroke volume with low or normal pressure in the pulmonary artery. Infection and increase in temperature often seemed to be the precipitating factors of manifest shock. After administration of colloids there was an increase in both the stroke volume and the pressure in the pulmonary artery. Patients in the second group had a small stroke volume with high mean pressure in the pulmonary artery, exceeding 16 mm. Hg, and signs of myocardial involvement or disturbances in cardiac rhythm in some patients, possibly due to hypokalemia. With further increase in pulmonary arterial pressure in this group the stroke volume decreased. By digitalis or potassium therapy, with restrictive administration of colloids, the condition was sometimes improved.

The dissimilar treatment in the two groups emphasized the importance of detailed circulation studies in these patients with severe burns. Only one of five patients with pulmonary edema had a markedly increased pressure in the pulmonary artery. Overloading of the circulation by excessive fluid therapy probably played a subordinate role as a cause of pulmonary edema. A capillary lesion in the lungs due to lower respiratory tract burn, hypoxemia, humoral factors or infections, defective colloidal osmosis, or myocardial damage were probably of greater importance. Respiratory intrathoracic pressure variations gave a relative measure of the mechanical properties of the lungs, and great variations in pressure were seen in these cases of pulmonary edema. The authors found that the expected correlations between the cardiac output and the oxygen uptake, and between the pulse rate, corrected for temperature, and the stroke volume, had direct clinical implications. The former illustrated the main possibilities of influencing the hypoxemia of the tissues.

The hypoxia and reduced oxygen uptake in some tissues, which results from a small cardiac output and a more or less localized peripheral vasoconstriction with diminished blood flow, may be expected to be improved only slightly by inhalation of oxygen, since the oxygenation of the arterial blood is already satisfactory. Measures aimed at increasing the cardiac output form the necessary treatment in these patients, while for the pulmonary complications with reduced oxygen saturation in the arterial blood the administration of oxygen is indicated. The latter shows that pulse rate is an important indicator of latent shock or circulatory failure. This is of special importance, because the arterial pressure, by compensatory mechanisms, is normal in many patients with latent shock. The significant correlation between the carbon dioxide tension in the arterial blood and the bicarbonate concentration shows that metabolic acidosis is a common cause of the hyperventilation which is usually seen in patients with severe burns.

Postoperative Dextrose Infusion.—The concentration of the unesterified fatty acids of plasma is increased on the first postoperative day, while the glyceride and phospholipid levels of the plasma are decreased. The rise in the plasma unesterified fatty acid level has been interpreted as a manifestation of increased mobilization of fat from the fat depots. L. B. Wadström (*Acta chir. scandinav.* 116:395-400, 1958/1959) studied a series of six patients to determine whether or not the infusion of dextrose, which is often given postoperatively, affected the altered lipid composition of plasma associated with surgical trauma. The four women patients were operated on for gallstones and the two men for gastric ulcer. No complications attended the operations. The infusion of dextrose was found to counteract the increased concentration of fatty acids in plasma after surgical trauma. The effect was inversely related to the blood sugar level and persisted as long as the infusion continued but was no longer demonstrable one hour after the administration was stopped.

During infusion, the dextrose produced no detectable effect on the plasma glyceride or phospholipid levels. Under normal conditions a relationship has been observed between the glyceride level of plasma and carbohydrate metabolism. A decrease in the glyceride-rich lipoproteins was noted in other patients after the oral intake of carbohydrates. In the present series dextrose did not exert any effect

on the postoperative glyceride level of plasma. The author commented that perhaps the amount of dextrose given might have been too small to produce any effect. They received only 100 calories in two hours, while in the earlier series cited and composed of healthy persons, 1,000 calories was given over a period of four hours. The present report demonstrated no changes in phospholipid concentration after the infusion of dextrose. Here, as for the glycerides, the explanation might be that the amounts of calories given in the two studies differed widely.

Esophageal Perforation.—Perforation of the esophagus is a serious injury that occurs most frequently in connection with endoscopy and dilation treatment. The use of these procedures is increasing. Rietz and Werner (*Acta chir. scandinav.* 116:401-410, 1958/1959) analyzed a series of 24 patients who had esophageal perforations, 7 of which proved fatal. Of these two died of general sepsis, one of empyema, one of mediastinitis with empyema, one of complications arising from too many blood transfusions, and two of mediastinal abscesses.

The important factor in traumatic perforation of the esophagus is the presence of a rupture of such dimensions as to permit esophageal or gastric contents to contaminate the mediastinum. Full knowledge of the topography of the cervical fasciae and the anatomy of the mediastinum is necessary for a correct interpretation of the symptoms and for adequate therapy. A recent perforation should be regarded as a surgical emergency. As in perforated ulcer, the earlier the operation is performed the better is the prognosis. The most favorable period is within 6 hours, although it has been found technically possible to close the perforation after 20 hours. Several of the patients in the present series were operated on long after the perforation had occurred, when pronounced inflammatory changes precluded primary suture. Consequently, treatment had to be directed to such secondary manifestations as mediastinal abscesses and empyema. This was reflected in the high mortality.

Hypoproteinemia and Gastric Carcinoma.—A study of 67 patients with gastric carcinoma was undertaken by H. Sunzel (*Acta chir. scandinav.* 116:429-436, 1958/1959) in order to clarify the nature of the preoperative hypoproteinemia associated with that condition. Hypoproteinemia does not appear to be specific to cancer but may result from nutritional deficiency and pathological loss of protein. In patients with a history suggestive of protein depletion the operative mortality was found to be five times as high as in those without any such history of protein disorder. The excessive mortality was due to poor healing of the anastomosis and increased susceptibility to infection. Malignant neoplastic disease is often characterized by a decreased concentration of total serum protein, accompanied by a relative increase in fibrinogen and globulin levels. The protein abnormality increases in proportion to the extent of the disease. It is of great practical importance to determine whether or not hypoproteinemia in cancer patients is produced by a specific effect of the growth and to study its resistance to preoperative therapy.

The two sexes were about equally represented in the 67 undergoing partial or total gastrectomy for carcinoma of the stomach, and preoperative hypoproteinemia was observed in 34 instances. Inadequate intake owing to mechanical obstruction and excessive loss of protein due to hemorrhage appeared to be responsible for the hypoproteinemia. Patients with a history of protein depletion—not always reflected in the serum protein level because of coexistent dehydration—had an operative death rate of 31% as opposed to a rate of 6% in those in whom no similar history was recorded. It does not suffice to administer only protein or amino acids in the hope of restoring optimal protein synthesis. The administration of protein without accompanying calories to an emaciated patient results only in the utilization of the protein chiefly for energy requirements. Modern principles of treatment with a high-calorie diet plus protein may be capable of partially or wholly restoring the protein deficit in cancer patients before time leads to deterioration of the patient's condition due to the basic malignant disease.

UNITED KINGDOM

Stricter Test for Disability Urged.—A sterner line in assessing disability was suggested by Dr. H. C. J. L'Etang in the *Practitioner*. He cited the case of many men whose deafness, poor sight, disabled limbs, and diseases did not prevent their reaching the top in sports and asked whether the conscientious physician could definitely state that loss, or malfunction, of a limb, or special sense organ, invariably led to disability.

Echoencephalography.—An apparatus employing ultrasonic waves for diagnostic purposes was designed by Gordon (*Brit. M. J.* 1:1500, 1959). It is a modification of that used for detecting and locating submarines (asdic) and for detecting flaws in large masses of metal. The physical principle underlying the use of ultrasonic waves is the piezoelectric effect, that is the result of an electric charge on opposing surfaces of a crystal when under stress. At the frequencies employed in medicine the ultrasonic rays are produced by crystals of quartz or barium titanate. The rays are closer in type to sound waves than to radio or x-rays. They are backward and forward movements of the molecules of the transmitting medium.

The production of echoes depends on the rays traversing an interface between two media in which the velocities of the rays differ. The factors affecting the velocity of propagation are complex, and include density and elasticity. The densities of cerebrospinal fluid and brain are almost identical, but their elasticities differ greatly, and it is thus possible to obtain echoes from the surface of the brain without using an artificial contrast medium. The great difference between the densities of air and cerebrospinal fluid causes such a difference in velocities that almost complete reflection of ultrasonic rays occurs at any interface between them. The echoes returning from reflecting surfaces produce radio-frequency electrical pulses of the order of microvolts, and these are greatly amplified, then rectified, and partly smoothed so that they can be displayed on an oscilloscope as an upward deviation of the tracing.

At present, the scope of echoencephalography is limited to demonstrating enlargement of the ventricles and displacements of the brain, which should be of value in assessing the extent of cerebral damage in severe head injuries, and in examining patients in whom angiography or pneumography is inadvisable. It also provides a method of observing the progress of inoperable or postoperative cases more often than is practicable radiologically. In other parts of the body, such as the pleura, the diagnostic use of ultrasonic rays should be of value, as in the detection of collections of fluid within layers of pleural exudate.

Sputum Survey.—Hitherto, the prevalence of chronic nonspecific pulmonary disease has been studied by death rates, sickness certification, and surveys of respiratory symptoms. Elmes and co-workers approached the problem by a sputum survey of a selected group of workers (*Lancet* 1:1241, 1959). Postmen and female clerical staff working for the post office, in the age group 40 to 60 years, were issued sputum jars. They were asked to return all sputum coughed up within an hour of rising in the morning and the specimens were examined macroscopically, bacteriologically, and cytologically.

The survey revealed that 50% of the men and 25% of the women regularly expectorated and that in 25% of the men and 12.5% of the women, the sputum was purulent, indicating that they had persistent bronchial disease, probably chronic bronchitis. More sputum was produced in the winter months, and more with increasing age in the men, but not in the women. Of the organisms most frequently cultured in significant numbers were Hemophilus influenzae and Streptococcus pneumoniae. The presence of heavy growths of these organisms was remarkably constant, except in the summer specimens, from the women. There was a strongly positive association between a heavy growth of H. influenzae and the presence of pus in the sputum. Those subjects who produced more than 4 ml. of sputum in the first hour after rising had, on the average, a reduced breathing capacity. One patient with sputum positive for Mycobacterium tuberculosis was discovered through the survey.

High-Voltage Radiotherapy.—Treatment by high-voltage radiation is being extended. After a recommendation by the Central Health Services Council's Cancer and Radiotherapy Advisory Committee, the Ministry of Health made provision for 10 more linear accelerators in England and Wales and 2 for Scotland. Irradiation at several million volts reduces harmful effects on skin and bone, and the greater penetrating power of these high-voltage rays permits the use of less radiation for a given dose to the tumor. More equipment is needed in the hospitals to derive the maximum benefit from this form of irradiation. More cancer patients are surviving and as the life span is increasing more people are living in the cancer age group. The faculty of radiologists has therefore advocated the provision of more high-voltage apparatus. It recommends a minimum of 20 to 30 linear accelerators for England and Wales, and a proportionate number for Scotland and Northern Ireland.

Attenuated Poliovirus Vaccine.—A team of workers from the University of Malaya and the medical departments of Singapore (*British Medical Journal*, June 20, 1959) reported an epidemic outbreak of poliomyelitis due to a type 1 strain of virus that occurred in Singapore late in 1958. A definite predilection for older children was noticed. Previous outbreaks had always been chiefly in children 2 or 3 years old. This might indicate that Singapore is changing from an area where poliomyelitis is endemic and cases of the infantile type occur to one in which epidemics might be expected and older children would be involved. In this epidemic the government offered an attenuated type 2 vaccine, which was supplied by Dr. Albert Sabin (Cincinnati) for voluntary vaccination. Of 198,965 children vaccinated only 6 developed paralysis. In the same period (one week after the start of the vaccination campaign to the end of the epidemic) there were 179 paralytic type 1 cases in the 300,000 nonvaccinated children of the same age group.

No untoward effects followed the vaccination and not a case of type 2 paralysis occurred in those vaccinated. Antibody response to the vaccine was highly satisfactory, although a small proportion of children in the younger age groups failed to develop detectable antibodies after vaccination. Some of the virus strains excreted by those vaccinated showed slight increases in virulence to monkeys tested by intraspinal inoculation. This was not a progressive phenomenon, and strains isolated from contacts, where it could be assumed that at

least one human passage had taken place, were no more virulent than those obtained directly from the vaccinated. Only one case of type 2 paralytic poliomyelitis occurred in a nonvaccinated child, and, as it was shown that wild virulent type 2 strains were circulating in a neighboring community, it was believed that this case could have resulted from infection with such a wild strain.

Hospital Lay Officials Dictating to Physicians.—Hospital lay administrators who dictate to physicians what drugs they should prescribe were attacked at the conference of the Confederation of Health Service Employees. A resolution calling attention to the growing tendency in hospitals for lay administrators to control medical and nursing responsibilities was remitted to the executive. Such practices lower the status of the medical and nursing professions and could be injurious to patients. Mr. C. E. Wood, objecting to the dictatorial ways of local officials, said that all the lay administrators thought they were ministers of health and could interpret the National Health Service regulations in whatever way they chose.

A Five-Year Study of a General Practice.—A supplement to the *British Medical Journal* of June 20 includes a memorandum by Drs. Alistair and George Muir of Grangemouth. The keeping of careful records and statistics, with detailed costs and expenses of their practice led them to conclude that (1) the maximal list in a healthy, middle-class, compact and prosperous practice should be 2,000 patients per physician; (2) this list demands an average six-day working week of 50 hours from each physician; (3) with a practice of two doctors and a total list of 4,000 patients each member is either on call or working more than 80 hours a week; (4) efficient service to patients increases their demands and requires increasingly large expenditures of time and money; (5) in order to maintain a turnover of even 7 patients per hour in the office, a physician must work under a degree of tension that cannot be good for his health or emotions, and this speed cannot ideally cover the needs of the patient; this leads to a less adequate service than could be rendered in other circumstances; (6) with a list of 4,000 patients and two physicians it is necessary to employ an assistant, or take on another partner, in order to keep up a reasonable standard of work; (7) the remuneration is unrealistic considering the hours worked and responsibilities assumed, and by comparison with the reward of other trades and professions; (8) practice expenses must, automatically, be high if high quality standards are to be maintained; (9) the premises on which the National Health Service was based are discredited by their own figures, which show that 57.8% of the patients receive some treatment each year; and (10) the more comprehensive the service offered, the greater are the demands made by the patients, and the more critical they become of the results; this is reflected in an increasing drug bill.

The practice of these two doctors is conducted from a suite with two examining rooms, two waiting rooms, and a consulting room located in the home of one of the principals. Only maintenance of this portion of the house relates to practice expenses. The doctors' cars are small (not over 10 horsepower). A receptionist and a cleaner are employed. Practice expenses are high (38.7% of the gross income), but no higher than is compatible with offering decent comfort and efficient administration to their patients. The reward of $4,416 per annum for each principal, averaged over the past five years, is hardly a fair return for the treatment of several thousand patients.

The authors conclude that the maximal lists should be reduced drastically and that this, plus the inadequacy of the salary, fosters a temptation to skimp practice expenses necessary to patients' comfort and efficient administration and breeds a sense of resentment toward the entire system. Both authors admit having a private income without which they could not live.

Medical Aspects of Boxing.—An article in the *Lancet* (referred to in this column Aug. 15, 1959) condemning boxing as a dangerous sport and suggesting its legal abolition caused widespread controversy in both the lay and the medical press. The boxing associations and their medical advisers consider that boxing is no more injurious to its participants than other sports and is, in fact, less so than rugger or ice hockey. In a scientific inquiry into what happens in the punch-drunk boxer's brain Prof. Peter Daniel and Dr. Sabine Strich, of the Maudsley Hospital, London, pointed out that, because of the chronic course and long latent interval which precedes the onset of symptoms, few pathological studies have been made of the nervous system of boxers, particularly those who have suffered from punch-drunkenness. They suspect that many punch-drunk boxers die in mental hospitals, where facilities for detailed pathological examinations of the nervous system are usually not available and they are, therefore, asking for the brains of any punch-drunk patients for examination and also for those of boxers dying in, or just after, a fight.

Fourteen honorary medical officers of the Amateur Boxing Association replied to the *Lancet*. They claimed that there have been only seven deaths in 13 years in the British boxing ring and that this record compares favorably with that of other sports. With regard to the mental deterioration that is believed to occur in boxers, they pointed out that Len Harvey had 400 major bouts and that his mentality is as normal as that of any man of his age and social position. The medical officers stated that they had

made 57 electroencephalograms in three years on amateur boxers who had severe concussion. Examination after one month revealed no abnormality. In 30 years they saw only two cases of detached retina, and these were operated on successfully. They claimed that only one blow in 10 strikes the head and that only one bout in 60 ends in a knockout.

Airlines Accused of Negligence.—In an editorial the *Lancet* accused the airlines of jeopardizing passengers' lives for money because they declined to fit backward-facing seats in civil aircraft. The reason given is that this would reduce the payload of aircraft. The narrow abdominal belt provided was also criticized because it does not restrain the trunk, and, if there is a sudden stop, the head, trunk, and lower limbs are thrown forward and downward and are likely to be injured by striking the seat in front. In addition, the narrow belt can produce severe intra-abdominal or intrathoracic injuries because a great pressure is applied over a small area. Decelerative injuries do not occur when the area of restraint is sufficiently spread, as in the backward-facing seat. The R. A. F. has been persuaded of the advantages of backward-facing seats, and has fitted them in all transport command and charter aircraft since the last war. It is unlikely that passengers would use, or that aircraft companies would fit, the elaborate harness worn by military aircraft crews. The *Lancet* concluded that the world's airlines are influenced more by economic than by safety factors.

Doctors and Publicity.—The *Medical Press* suggested revising the doctors' code of ethics based on the realities of today and not on the conditions of 100 years ago. The ethics of the profession are largely based on proposals made by the General Medical Council in 1858. Revision is called for because of the confusion at present prevailing over anonymity in the popular press, broadcasting, and television. Some physicians allow their names to be used, while others remain anonymous. The *Medical Press* pointed out that if doctors are members of parliament, writers, or leading athletes, as a few of them are, they can hardly escape publicity. Society has a right to know what is going on in developments in medicine and to know something about the men concerned. So long as a doctor does not make use of what opportunities come his way to take an unfair advantage of his colleagues or to misrepresent or betray the profession there is no reason why he should not appear on television if asked, or write under his own name if he feels so inclined. The half-enforced ban that exists does nothing to deter persons who might profitably be deterred, while intimidating others whose voices might, with advantage, be heard. Now that physicians work in a National Health Service, one result of which is that their affairs can become at any time the subject of discussion or attack in Parliament, it is time that they shed their inhibitions and got used to the sound of their own voices.

Sir Harold Gillies, the pioneer of plastic surgery, stated that he refused a Sunday newspaper offer of $18,200 for a series of six articles on his life. These articles would have been harmless and the offer was prodigious in terms of the effort involved in the work. He subsequently wondered if he had been poorly advised. Sir Harold believes that the answer to medical publicity lies in educating the press to the standards of the medical profession. As a means of spreading among the public, including the medical profession, the great advances in medicine and surgery, properly controlled publicity should be welcomed by doctors.

WORLD HEALTH ORGANIZATION

World Health Assembly.—The twelfth World Health Assembly in Geneva in May adopted the program of work for 1960, along with a regular budget of $16,918,700. Activities planned include the control of major communicable diseases, such as tuberculosis and leprosy, and eradication campaigns against malaria and smallpox. Expansion of work and research in the fields of virus diseases, nutrition, and health statistics is included in the program, as well as continuation of activities in such traditional fields as quarantine, standardization of drugs, education and training of health personnel, and exchange of information. WHO is to enlarge its research activities to fill the gaps in coordination and communication among research workers throughout the world.

The main emphasis will be on such problems as the conquest of communicable diseases. Particular attention will be paid to the investigation of factors contributing to the incidence of heart disease and cancer. The assembly recommended that countries give priority to the provision of safe and adequate water supplies. WHO is to provide leadership in a coordinated global program of community water supply and to provide technical and advisory services when so requested by governments. Safe and adequate water supplies are essential to the protection and improvement of health and are indispensable for economic and social development. Within the past three years 56 countries and territories have suffered epidemics of smallpox. The assembly asked for intensive campaigns to rid the world of this dangerous, disfiguring, and expensive disease, the cure for which has been known for more than 150 years.

The malaria eradication program is progressing well, but funds are lacking to finance WHO's continuing leadership in this global campaign. Governments, industry, foundations, and others were urged to join with WHO in eradicating malaria by contributing to the World Malaria Fund.

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V.

CORRESPONDENCE

DETERMINATION OF OVULATION TIME

To the Editor:—I believe the paper "Statistical Method for Determination of Ovulation Time in Women" by Murray (*J. A. M. A.* 170:42-43 [May 2] 1959) is based on a series of erroneous concepts which need to be clarified in order not to perpetuate the confusion which obscures the relationship in time between ovulation and menstruation. The author equates the day of insemination with the day of ovulation. This is an assumption for which, except for a few doubtful observations, there is no proof in the human female (Bergman: *Acta. Obst. et gynec. scandinav.* [supp. 4] 29:1, 1950). He assumes the length of the menstrual cycle to be an independent variable on which, correspondingly, the length of the preovulatory or postmenstrual phase depends. In fact, the relationship is inverse; the length of the menstrual cycle depends on the length of the preovulatory phase (Hartman: *World of Obst. Gynec.* 7:323, 1955; Palmer: Diagnostic Use of Basal Body Temperature, in Gynecology and Obstetrics, edited by Davis, Hagerstown, Md., W. F. Prior Co., Inc., 1953; Tompkins: Interpretation of the Basal Body Temperature Curves, in Proceedings: Conference on Diagnosis in Sterility, Sponsored by National Committee on Maternal Health, Jan. 26-27, 1945, Springfield, Ill., Charles C Thomas, Publisher, 1946; Vollman: Individual Record of 324 Menstrual Cycles, *Anat. Rec.* 133:347, 1959). This association was first clearly expressed by Sorel (*Gaz. med. de Picardie* 4:167, 1886) and has since been confirmed by independent observers and with a diversity of techniques (hormone assay, histology of the uterine mucosa, and vaginal cytology).

In his equation of regression the author uses as one variable the average length of the menstrual cycle. Without knowing the number of cycles and the degree of their variability on which the average is based, it is impossible to discuss a possible linear association (Vincent: *Population* 11:59 [Jan.-March] 1956). Though he claims to have established a linear association between the length of preovulatory phase and the menstrual cycle, the author contends that ovulation "occurs between the 10th and 15th day for nearly all cases regardless of the length of the menstrual cycle." I am unable to reconcile these two contradictory statements. Without justification the author truncates his data on the menstrual cycle by excluding cycles shorter than 23 and longer than 34 days. This is a doubtful and dangerous procedure. Menstrual cycles shorter than 23 and longer than 34 days occur rather frequently (Vollman: *Gynaecologia* 142:310 [Nov.] 1956; *Anat. Rec.* 133:347, 1959). A reliable prognostic test for ovulation in woman is urgently needed. It may not be compensated for by doubtful statistics.

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The above comment was referred to the author of the article cited, and he has submitted the following reply.

To the Editor:—I should like to offer the following comments on Dr. Vollman's letter. First, in simple linear correlation there is no implication of a cause and effect relationship merely because one variable is referred to as the independent variable. Actually, the coefficient of correlation is identical regardless of which is made dependent and which independent. Hence, the association observed in the Sevag-Colton data would be the same even if the length of the cycle were, as Dr. Vollman suggests, the dependent rather than the independent variable. A variable is assigned the independent position in the equation because one plans to use it to estimate the other. If one is seeking to achieve pregnancies it seems likely that he will try to estimate the most favorable day for insemination or coitus, using the length of the menstrual cycle as the independent variable.

Second, the fact that averages were used for the length of the cycle results in a reduction in the variance about the regression line, but it does not mean that the relationship would not have been linear had individual observations been used.

Third, I am not certain what Dr. Vollman means when he says he is "unable to reconcile these two contradictory statements." In my paper it is stated that ovulation "occurs between the 10th and 15th day for nearly all cases regardless of the length of the cycle" which is merely an observation of fact. However, the paper continues by pointing out that a more critical determination can be made by using the regression equation. This is no different from saying that nearly all men weigh between

125 and 225 lb., but that a better estimate of the weight of a given individual can be made if one knows his height. (I assume that Dr. Vollman will accept my thesis that there is a correlation between height and weight in adult males.)

Finally, by truncating the data to exclude those cases with cycles shorter than 23 days or longer than 34 days, I am not implying that such cycles do not exist, perhaps even frequently. The article merely states that they were excluded in this case because they appeared to be unusual from the standpoint of the problem. Their exclusion merely limits the validity of the regression equation to those cases where the cycles lie in the range of 23 to 34 days. As in any correlation analysis, the line obtained is valid only within the limits of the data and for the group studied or for groups of which it is typical.

Donald S. Murray, Ph.D.
Philadelphia.
University of Pennsylvania

INTRATHECAL USE OF METHYLENE BLUE

To the Editor:—Dr. Joseph Evans (*J. A. M. A.* 169:528 [Jan. 31] 1959) recently communicated a warning on the use of methylene blue intrathecally and reported a case of his own that resulted in paraplegia. I wonder how the ampul of methylene blue was stored and how it was sterilized. Ampuls of this drug are usually kept in a detergent solution or alcohol or phenol solution so as to be ready for immediate use. Microscopic cracks in ampuls can allow entrance of these neurotoxic solutions without any apparent external sign. Spinal anesthesia has been held responsible for paraplegia when the storage solution was actually at fault. Autoclaving of all ampuls that are to be administered intrathecally is *sine qua non*. They should never be immersed in solutions. It is interesting to see the similarity in the condemnation of spinal anesthesia and of methylene blue in this report.

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The above comment was referred to the author of the article cited, and he has submitted the following reply.

To the Editor:—The ampul of methylene blue used in our patient was not kept in a detergent solution, in alcohol, or in phenol; it was used as provided by the manufacturer, the ampul head merely being wiped with iodine before being broken open. I believe, therefore, there is no similarity to the condemnation of spinal anesthesia as is suggested by Dr. Sivak. We are attempting to determine whether the acidity of the staining material may not be the responsible factor, even though 1 cc. of it was diluted with 23 cc. of cerebrospinal fluid.

Joseph P. Evans, M.D.
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Chicago 37.

SARCOMA OF LUNG IN AN INFANT

To the Editor:—The abstract of the report of a child 33 months of age with primary fibrosarcoma of the lung (*J. A. M. A.* 170:1243 [July 4] 1959) has come to my attention, as well as the statement contained therein to the effect that "this is the youngest case of this type of sarcoma of the lung ever recorded." There is on record a case of an infant from whom a fibrosarcoma of lung was removed at the age of 2 days (Robb, D., *Brit. J. Surg.* 46:173 [Sept.] 1958). This patient was reported as being alive and making good progress 10 months after the operation. This information is being submitted so that the facts as already documented in The Journal may be corrected.

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MEDICAL FILM REVIEWS

Removal of Ciliary Body Tumor (Benign Melanoma): 16 mm., color, sound, showing time 6 minutes. Prepared in 1958 by and procurable on loan from Arthur Alexander Knapp, M.D., 907 Fifth Ave., New York 21.

This film shows that a tumor in the "danger zone," an area of dire surgical complications, can be removed successfully. This is a true surgical achievement but technically the film is not up to the quality of the surgery demonstrated. It would seem that the photography, though well done, is optically so distant from the operative site that the details of the surgical procedure are masked. If the aim of the film is to demonstrate the technique, one must conclude that it falls short as a teaching film. In summary, one must say that the subject matter is quite informative as are the drawings, but the remote view of the observer detracts considerably from the value of this film and what can be learned from it.

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V.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Clinical Experiences with Digoxin. L. A. Soloff and J. Zatuchni. Am. Heart J. 57:674-683 (May) 1959 [St. Louis].

The purpose of this study was to determine the effectiveness, safety, and versatility of digoxin in restoring and maintaining cardiac compensation in hospitalized and ambulatory patients. The effectiveness of the intravenous administration of digoxin in the form of Lanoxin for emergency use was determined in 6 patients in acute congestive cardiac failure with atrial fibrillation. To determine the effectiveness of digitalization by the intramuscular route, 1.5 mg. of Lanoxin was injected into 3 patients with acute congestive cardiac failure and atrial fibrillation. The usefulness of digoxin administered intramuscularly was determined in 9 patients. The effectiveness of oral digitalization with Lanoxin was investigated in 40 hospitalized patients in congestive cardiac failure with atrial fibrillation. To determine the effectiveness of digoxin in maintaining compensation, as well as to learn the optimal maintenance dose, observations were made on 40 ambulatory patients.

The results of these studies indicate that Lanoxin is a safe, effective, and versatile preparation for oral, intramuscular, and intravenous use. A safe initial digitalizing dose appears to be either 2 mg. orally or 1.5 mg. intravenously or intramuscularly, unless acute myocardial infarction is present or suspected; under such circumstances, half of each of these doses is used. A dose of 0.75 mg. intramuscularly is safe and usually effective in those in whom failure develops abruptly after previous adequate maintenance. Individualization of dosage is started 24 hours after the initial dose. If the fall in ventricular rate is satisfactory, and nausea is absent, the patient is placed on a maintenance dose of 0.5 mg. If nausea is present, which is extremely rare, no further digoxin is given until this symptom disappears. A maintenance dose of 0.25 mg. is then started, and is increased to 0.5 mg. if the ventricular rate is regarded as too high. If the ventricular rate and pulse deficit have not been corrected satisfactorily, 0.25 mg. is given every 6 hours until such a response occurs or toxic symptoms appear before starting the maintenance dose. Only in obviously urgent circumstances is individualization of dosage begun 6 hours after the initial dose.

The average maintenance dose of digoxin is 0.25 to 0.75 mg. No difficulty was encountered in maintaining patients on digoxin in spite of its fairly rapid dissipation. Although there is considerable overlapping, patients with coronary disease usually require the smallest dose, the rheumatic patients the largest dose, and the hypertensive patients a mean of the two. An intramuscular maintenance dose of digoxin identical with the oral dose may be substituted without any noticeable change in the drug's effectiveness. Nausea is almost always the initial manifestation of toxicity with digoxin. Only when severe depletion of potassium is present may cardiotoxic effects occur in the absence of gastrointestinal symptoms. It is necessary to differentiate a systemic from a local emetic action of digitalis. Time may often be used as a deciding factor to make this distinction. The authors considered instances in which nausea occurred within 30 minutes of ingestion of the drug and was of too short duration to be due to local gastric distress. Giving the total maintenance dose in 2 equal amounts, morning and evening, corrected the condition.

Clinical and Physiologic Studies in Ebstein's Malformation. W. R. Livesay. Am. Heart J. 57:701-711 (May) 1959 [St. Louis].

The basic morphologic defect in Ebstein's malformation is a downward displacement of one or more leaflets of the tricuspid valve, so that the upper portion of the right ventricular cavity is incorporated into the right atrium and functions as part of the atrial cavity. The distal right ventricular cavity then becomes filled by a membranous sail-like sheet as a result of fusion of one or more of the tricuspid leaflets, leaving only a small chamber at the apex and the infundibular portion. A case is presented to illustrate this lesion. The patient was a 34-year-old woman whose physical capabilities as a child were limited because of exertional breathlessness. Nail-bed cyanosis became apparent first at the age of 12, but not until the age of 15 was she told that a heart murmur was present. In spite of the complaint of fatigability, she worked as a tele-

The place of publication of the periodicals appears in brackets preceding each abstract.

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phone operator, married, and bore one child at the age of 26. Because of a gross hemoptysis in June, 1953, she came under medical surveillance again. From this time on she showed progressive deterioration, with repeated small hemoptyses, almost daily occurrences of sudden rapid heart action, and signs of cardiac failure. Sudden death occurred during sleep in June, 1954, when she was 35 years old. The postmortem examination revealed Ebstein's malformation associated with patent foramen ovale, which served as a shunt.

Ebstein's anomaly was first described in 1866. Up to 1951 the total number of cases reported was 31; now the total is about 90. Symptoms are often mild, and some patients have no complaints. The feature of relatively good exercise tolerance in the presence of considerable cardiomegaly may be of diagnostic aid. Cardiac arrhythmias are considered frequent, and about one-third of the patients reported have shown paroxysmal atrial tachycardia, atrial flutter, or fibrillation. Because so many patients die suddenly, it is most likely that a disturbance in rhythm is implicated as the final event. Some die in congestive heart failure. Cerebral deaths as a result of paradoxical embolism through the coexisting defect in the atrial septum have claimed a few. Too frequently in recent years death has occurred during surgery as the result of an erroneous diagnosis of Fallot's tetralogy. Evidently, the disease may also be benign and compatible with considerable longevity, since the malformation has been reported in a 79-year-old woman. On auscultation the presence of the loud third heart sound appears to be the finding of sufficient distinction and incidence to be of real value in the diagnosis when fitted in with the other clinical findings of Ebstein's malformation. Electrocardiography reveals in the majority of patients an atypical right bundle-branch block. With modern diagnostic techniques the diagnosis can be made during life. The main diagnostic criteria are late or absent cyanosis, roentgenologic evidence of right atrial and right ventricular enlargement without signs of pulmonary vascular congestion, and pressures in the pulmonary artery and right ventricle which are within the normal range.

Role of Emotional Stress Preceding Coronary Occlusion. F. Dreyfuss. Am. J. Cardiol. 3:590-596 (May) 1959 [New York].

The author studied 41 patients with coronary occlusion in an attempt to determine the role of emotional factors as precipitating causes of an attack of coronary occlusion. In 18 of the 41 patients emotional stress could not be considered to have played a role during the months, weeks, or days before the infarction. In the remaining 23 patients a well-substantiated history of emotional stress preceding the coronary occlusion was elicited. Three patterns of such stress were observed as follows. Acute short-term stress had occurred in 3 patients; chronic or subacute stress, frequently complicated by acute stress immediately preceding the coronary occlusion, had occurred in 11 patients; and emotional stress as a contributory factor to other stress mechanisms had occurred in 9 patients. The pattern of subacute and acute superimposed emotional trauma seemed to occur much more frequently among patients between the ages of 30 and 60 years than among those over 60. It is suggested that thrombogenesis be distinguished from atherogenesis in order to further better understanding of coronary artery disease and coronary thrombosis. An increased thrombotic tendency may be of decisive influence in coronary occlusion in the younger age group as potentially precipitated by stress mechanisms operating on blood clotting. Atherogenesis, on the other hand, represents the aspect of a usually slow vascular degenerative disorder which has to be attacked mainly on a long-term basis and which may account for coronary occlusion in patients of more advanced age.

Heart and Hyperthyroidism. H. A. Baro, J. R. Echeverría and E. P. G. Baro. Prensa méd. argent. 45:3677-3680 (Nov. 21) 1958 (In Spanish) [Buenos Aires].

Hyperthyroidism, in the presence of coronary arteriosclerosis, may increase the difficulty of restoring normal rhythm in a heart recovering after a period of decompensation. A man, 42 years old, had a myocardial infarct healed by rest. When activity was resumed, the patient, on 3 different occasions while receiving digitalis, developed symptoms of decompensation. All the cardiac symptoms but tachycardia were controlled by rest, administration of digitalis and mercurial diuretics, and a diet without salt. The patient started to suffer with crises of precordial pain during the night. Pain was controlled only by the administration of opiates. The patient had a moderate exophthalmos, tremor of the fingers, persistent tachycardia (which did not respond to rest or to digitalis), and an increased basal metabolic rate. Digitalis was withdrawn, and propylthiouracil therapy was started. The latter drug was given in daily doses of 250 mg. for 10 days and 200 mg. for 15 days; 150 mg. a day was given as a maintenance dose thereafter. Vitamin B_1 was administered concurrently with propylthiouracil. The crises of both precordial pain and tachycardia were controlled in a few days, and the patient resumed work. A follow-up for more than a year showed that the patient was well, had gained 12 kg. (27 lb.) in body weight, and had not had any more insufficiency of the heart or crises of precordial pain. The last electrocardiogram showed a healed myocardial infarct. The last roentgenogram of the chest showed that overload of the left ventricle had not been increased.

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A Critical Revision of the Concept of Tuberculoma of the Lung. G. Pozzi and L. Ribotto. Minerva med. 50:902-905 (March 28) 1959 (In Italian) [Turin, Italy].

The authors review the vast and frequently contrasting literature on tuberculoma of the lung, a special form of pulmonary tuberculosis of pseudotumorous aspect. They agree with Bariety who defined tuberculoma as a complex, circumscribed, caseous lesion created by foci which have developed successively. Tuberculoma is clinically asymptomatic, or has very few symptoms, and most of the time is discovered accidentally on roentgenologic examination. It may develop (*a*) from tuberculous foci of the lung, often even during the course of antibacterial treatment, (*b*) in the place of nodular foci that have regressed because of the effect of antibacterial substances, and (*c*) from foci cured with pneumothorax, especially when the collapse has been massive, but with little or no effect. Rather than an independent growth, tuberculoma represents the pseudotumorous aspect that some tuberculous growths of the lung assume on account of various biological factors involved. In contrast to Bariety, the authors attribute all the causes of the chronicity of tuberculosis, and therefore of the origin of tuberculoma, which is a typical example of this chronicity, to the direct or indirect effect of antibacterial drugs.

Relapse Rate in a Two-to-Eleven-Year Follow-up Study of Patients with Pulmonary Tuberculosis Treated With and Without Antimicrobials and Discharged from 1946 through 1955. E. Low. Am. Rev. Tuberc. 79:612-621 (May) 1959 [New York].

The author reports on 838 patients with pulmonary tuberculosis considered to have stable lesions both roentgenographically and bacteriologically and not necessitating surgical resection; 425 of these did not receive antituberculous chemotherapy, and 413 had chemotherapy. Of the 413 patients, 191 received chemotherapy for from 6 weeks to less than 6 months, 65 received combined treatment with streptomycin and aminosalicylic acid (PAS) for 6 months or more, and 157 received combined treatment with multiple drugs including isoniazid for 6 months or more. The follow-up period varied from 2 to 11 years. The cumulative relapse rate was computed by life-table procedure for each group. Over a follow-up period of 4 years computed for the 4 groups of patients, the cumulative relapse rate was 21.2% for those who did not receive chemotherapy, 17.1% for those who received chemotherapy for from 6 weeks to less than 6 months, 12.5% for those who received combined streptomycin-aminosalicylic acid therapy for 6 months or longer, and 8.8% for those who received multiple drug therapy containing isoniazid for 6 months or more.

Analysis of the relapses, which occurred after multiple drug chemotherapy for 6 months or more, with relation to extent of disease and to the combination and duration of chemotherapy revealed that patients did better with initial treatment with isoniazid and streptomycin given daily than with streptomycin and aminosalicylic acid, and that, in patients with cavitary disease, treatment with multiple drugs containing isoniazid is essential. Patients with minimal disease may do better with antituberculous drug therapy for more than 12 months, and those with advanced disease for more than 18 months. It is anticipated that, with the present routine of initial daily administration of isoniazid-streptomycin until sputum "conversion" has taken place, and if chemotherapy is continued for 18 months or longer, the relapse incidence in originally treated patients with bacilli susceptible to the 3 standard drugs will not be more than 1 or 2%.

Staphylococcic Infections and Their Treatment Today. J. Bøe. Tidsskr. norske lægefor. 79:455-459 (April 15) 1959 (In Norwegian) [Oslo].

The problem of staphylococcic infections and their treatment varies from day to day. These infections increase in relation to other pyogenic infections. One group of staphylococcic infections, seen in patients admitted for a grave condition, has not increased particularly in the last years, except perhaps for staphylococcic pneumonia in children. A second group is the group of increased hospital infections with staphylococci. Some of the new strains of staphylococci are strongly pathogenic, tend to spread, and have or acquire the quality of resisting antibiotics. The notorious Staphylococcus, type 80/81, has caused innumerable epidemics in hospitals in many lands and seems to persist longer in the nose and throat than other staphylococci. Between 70 ond 80% of the staphylococcic strains isolated in a hospital milieu are resistant to penicillin; the percentage of resistance in the general population is considerably lower. If a sensible policy in the use of antibiotics is followed and a given antibiotic is withheld from general use for a longer time, most of the staphylococcic strains will again be affectible by that antibiotic.

Many of the antibiotics in practical use today act on staphylococci and act well. As a rule, in the treatment of grave staphylococcic infections a bactericidal antibiotic is more certain than a bacteriostatic one. Penicillin is preeminently the best agent. It is more effective on sensitive strains than any other agent and also acts better on partly resistant strains, because it is atoxic and high blood concentrations can be attained. Streptomycin is also effective in staphylococcic infections with sensitive strains. Unfortunately many staphylococcic strains are resistant, and resistance can develop rapidly

during treatment. Streptomycin is bactericidal and can be combined with penicillin but is not suitable for longer treatment. While tetracycline acts well on sensitive strains, the number of resistant strains is increasing, as tetracycline is now in extensive use. Chloramphenicol is also an excellent agent. In Norway most of the staphylococcic strains still respond to erythromycin. Used in ordinary doses, erythromycin is bacteriostatic. Kanamycin affects the hearing and is somewhat nephrotoxic. It should, however, be possible to apply it in infections threatening life where there is resistance to other antibiotics.

Antibiotic treatment, especially in hospitals, is a community problem. In banal infections antibiotics which ought to be reserved for special use should not be applied extravagantly. Hospital infections with antibiotic-resistant staphylococci must be regarded as grave.

Serotonin Metabolism in Liver Disease. F. J. Borges, J. K. Merlis and S. P. Bessman. J. Clin. Invest. 38:715-719 (May) 1959 [New York].

Severe liver failure is frequently associated with serious disturbances of consciousness. This study was undertaken to determine whether the liver played any role in the metabolism of serotonin and whether such metabolism might be deranged by liver failure. Serotonin (5-hydroxytryptamine, 5-HT, enteramine) is widely distributed in animal tissues and has been shown to have marked pharmacological effects upon the gastrointestinal tract and cardiovascular system. Indirect evidence suggests that serotonin may play an important role in cerebral function. Previous reports and personal observations have shown a low normal excretion of 5-hydroxyindoleacetic acid (5-HIAA), the end-product of serotonin metabolism, in liver disease. The precursor of serotonin in the brain is apparently 5-hydroxytryptophan. In view of these facts, the possibility that severe liver disease, by affecting the production of 5-hydroxytryptophan, might alter brain function was investigated. Ten to 23 mg. of 5-hydroxy-DL-tryptophan (5-HTP), sterilized by dry heating and dissolved in 100 ml. of 0.85% sodium chloride solution, was given intravenously over a 30-minute period to 4 patients in severe hepatic coma, to 3 patients with abnormal electroencephalograms but not in hepatic coma, and to 1 normal individual. Electroencephalograms were recorded before, during, and after infusion. Where possible, 24-hour urine specimens were collected in 6-hour fractions, just prior to and immediately after 5-HTP infusion, and analyzed for 5-HIAA.

In all patients with hepatic coma, the slow activity diminished and the fast activity increased, altering the record in the direction of normal. In 3 patients with coma, not due to liver failure, and in 1 normal individual, there were no alterations in the electroencephalogram. Twenty-four hour urinary excretion of 5-HIAA accounted for 52% of the 5-hydroxy-L-tryptophan administered. No definite defect was observed in the ability of patients with liver disease to metabolize 5-hydroxytryptophan as compared with a control group. At the dosage levels utilized, infused 5-hydroxytryptophan produced no effect on blood serotonin. In patients with hepatic insufficiency, there was no change in tremors, mental confusion, or reflex activity. Abdominal discomfort and increased peristalsis were frequent.

Acute Intermittent Porphyria: A Study of 50 Cases. A. Goldberg. Quart. J. Med. 28:183-209 (April) 1959 [London].

The porphyria group of diseases includes acute intermittent porphyria, porphyria cutanea tarda, and congenital porphyria. Acute intermittent porphyria is the most important member of the group, and is clinically distinguishable from the other two by the dominance of gastrointestinal and neurological symptoms and the absence of skin photosensitivity. Patients with acute intermittent porphyria excrete in the urine porphobilinogen, a colorless chromogen which on the addition of Ehrlich's aldehyde reagent forms a red compound insoluble in chloroform. Porphobilinogen is never excreted in congenital porphyria, and rarely in porphyria cutanea tarda. The author studied the causation, natural history, and treatment of acute intermittent porphyria in 50 patients. A genetic survey was carried out on 11 affected families by the use of a paper-chromatographic method for the detection in urine of trace amounts of porphobilinogen. The survey confirmed the view that the disease is inherited as an irregular Mendelian dominant character. About 1 in 4 of the children of persons who excrete porphobilinogen may be expected to become similarly affected. Half of those carrying the abnormal gene may not excrete porphobilinogen, and 5 out of 18 subjects in states of remission did not have porphobilinogen in the urine.

Conditions which apparently precipitated or aggravated attacks were studied. Increased susceptibility to attacks was observed during the first trimester of pregnancy, and immediately after delivery. Infections precipitated attacks. Barbiturates, when given over prolonged periods to persons genetically disposed to the disease, precipitated attacks; when they were given during an attack the onset of paralysis was accelerated. Barbiturates which contained an allyl group appeared to be particularly dangerous. Analysis of the clinical features revealed that most patients had abdominal pain, accompanied by constipation, vomiting, or diarrhea. Ten patients were first seen because of pain in sites other than the abdomen, epileptic fits, or mental depression. Thirty-four patients had muscular paralysis or paresis. The paralysis was mostly of the lower motor neuron type, but 5 pa-

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tients had signs of involvement of the pyramidal tract. Nineteen patients had some form of sensory disturbance. Twenty-nine patients had mental symptoms. Hypertension was found in 28 patients, and tachycardia was a good index of the activity of the disease in 32 persons. Young patients had the severest form of the disease and were more likely to relapse. Some patients recovered quickly; others were left severely crippled, or even insane, after attacks. Complete restitution of physical and mental function occurred, but the recovery took up to 5 years in some cases. The mortality was 24%.

No member of a family in which there is a known case of porphyria should ever be given barbiturates. Steroid therapy should be instituted immediately after an attack is diagnosed. Ganglion-blocking drugs may be used to diminish hypertension. Because of vomiting, the water and electrolyte balance must be controlled. Chlorpromazine hydrochloride may be of value in the treatment of pain and psychoneurotic manifestations. Limb deformities must be prevented or treated.

It is suggested that in acute porphyria there exists a disturbance of pyrrole pigment metabolism in the nervous system, which is related to that known to exist in the liver. Demyelination is the pathological expression of this disturbance, and the clinical features may be explained entirely on a neurogenic basis.

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Polycythemia Vera: I. Clinical and Laboratory Manifestations. P. Calabresi and O. O. Meyer. Ann. Int. Med. 50:1182-1202 (May) 1959 [Lancaster, Pa.].

The authors describe (in 2 reports) their experiences with polycythemia vera at the University Hospitals in Madison, Wis. In this first report they deal with the clinical and laboratory manifestations in 100 patients observed since 1946, when radiophosphorus (P^{32}) became available for treatment in this disease. There is no single symptom, sign, or laboratory test that is pathognomonic of polycythemia vera; the diagnosis should be based on a composite clinical picture. The authors relied mostly on persistent elevation of erythrocyte counts and of hemoglobin, but hepatomegaly, splenomegaly, plethoric appearance, and elevated platelet and leukocyte counts served as supporting evidence. Although it has been estimated that the prediagnosis period is about 5 years in length, in these patients symptoms related to polycythemia were present, on the average, 2 years prior to diagnosis. The patients included 64 men and 36 women, and their ages ranged from 24 to 79 years (average, 54 years).

Weakness and/or fatigue and headache constituted the commonest symptoms, each occurring in slightly over half of the cases studied. These were followed by pain, swelling, or ulcerations in the extremities, dizziness or vertigo, and psychiatric disturbances. Symptoms like respiratory complaints (dyspnea and orthopnea), bleeding tendency, constipation, visual disturbances, paresthesias, and abdominal pain were observed in about one-third of the patients. One of the most nearly unique symptoms to be found in polycythemia vera is the presence of a peculiar form of pruritus, which is aggravated by exposure to heat, especially bathing with hot water. About half of the patients had this complaint.

The physical signs of polycythemia vera are mostly due to the increase in total blood volume and in erythrocytes. Hepatosplenomegaly and other signs of vascular congestion, such as facial plethora, distended retinal veins, peripheral vasodilatation and cyanosis, congestion of nasal and oral mucosa, and conjunctival congestion, were observed in various combinations, all the patients having one or several such signs. The importance of the laboratory data in confirming the diagnosis rests upon establishing the presence of an increased red blood cell mass and a normal arterial oxygen saturation. The erythrocyte count, hemoglobin level, and hematocrit are elevated. The highest erythrocyte count recorded was 12 million, but most writers agree that the greatest number of erythrocytes fell between 6 and 9 million.

The indexes of the erythrocytes for the most part are normal. The reticulocyte count usually is not elevated unless bleeding has occurred. Evidence of panmyelosis, which is often present, may furnish supportive evidence for the diagnosis. Polycythemia vera may mimic many clinical conditions. It should be considered in the differential diagnosis and evaluation of patients with hypertension. One may easily dismiss a ruddy patient with an elevated blood pressure and dizziness, headache, scotomata, dyspnea, and an emotional overlay as having "essential hypertension." Considering the possibility of polycythemia vera is unquestionably the hardest step in making the diagnosis. An important and challenging facet of polycythemia vera is its frequent association with certain seemingly unrelated conditions, such as peptic ulcer, gout, and hypernephroma. In these fields further research is needed.

Polycythemia Vera: II. Course and Therapy. P. Calabresi and O. O. Meyer. Ann. Int. Med. 50:1203-1216 (May) 1959 [Lancaster, Pa.].

This report is concerned with the clinical course of 97 of the 100 patients with polycythemia vera, who were discussed in the preceding paper, and who were treated with radiophosphorus (P^{32}). Although P^{32} has been used at the authors' hospital since 1946, the onset of the disease in some of the cases included in this series precedes this date by several years. The longest course was 23 years. Therapy in this clinic prior to the use of P^{32}

consisted mainly of venesections and the use of potassium arsenite (Fowler's) solution and of phenylhydrazine. No attempt is made to evaluate the efficacy of these regimens.

With the advent of P^{32} the following general treatment plan was adopted. The initial dose, ranging from 2 to 10 mc. (average, 6 mc.), was individualized according to body weight and erythrocyte count for each patient. The drug was administered orally in all but 6 instances, where the equivalent dose (75% of the oral dose) was injected intravenously. It has been the tendency in recent years to use smaller initial doses. The patient's hypervolemia was reduced immediately by a series of phlebotomies (500 cc. each) until the erythrocyte count fell below 6 million. Appointments were scheduled in the outpatient clinic at 6 weeks, 3 months, and 6 months from the beginning of therapy. Depending upon the response obtained, the patient was subsequently seen at 3-to-6-month intervals. Routine laboratory procedures were performed at these visits. A patient was considered to be in good control when his erythrocyte count did not exceed 6 million and he was asymptomatic.

Twenty-eight of the 97 patients have died, 6 of chronic granulocytic leukemia and 2 of myelofibrosis. It is difficult or even impossible to separate these 3 disorders. Furthermore, it does not appear that P^{32} has increased the occurrence of leukemia over what may be expected with the improved survival. The median survival in the present series was 11 years from onset of symptoms, and the median age at death was 65 years. This is similar to Lawrence's experience, and represents an improvement over figures reported with therapeutic methods other than P^{32} administration. Of 78 patients followed at regular intervals, 67 obtained successful remissions, defined as an absence of symptoms and erythrocyte counts of below 6 million for over one year. The remaining 11 all derived some benefit; of 6 who are still living, 3 are asymptomatic, and all have erythrocyte counts below 7 million. Leukocyte counts of over 25,000, relatively long duration of the disease process at time of therapy, and particularly marked splenomegaly were found to be of prognostic value in predicting a poorer response to P^{32}.

Alimentary Bleeding of Obscure Origin: A Follow-Up Study and Commentary. F. A. Jones, A. E. Read and J. L. Stubbe. Brit. M. J. 1:1138-1142 (May 2) 1959 [London].

Of 1,051 patients with hematemesis and melena admitted to the department of gastroenterology of the Central Middlesex Hospital in London between 1950 and 1955, 142 did not have any roentgenologic or other evidence of the source of bleeding. These 142 patients were followed up over a period of from 3 to 7 years. A positive diagnosis was subsequently made for 33 of them, but no diagnosis could be achieved for the remaining 109. Reexamination of the 33 patients with gastrointestinal bleeding of obscure origin revealed chronic gastric ulcer in 4, duodenal ulcer in 17, carcinoma of the stomach in 4, carcinoma of the colon in 3, carcinoma of the pancreas in 1, carcinoma of the small intestine in 2, Meckel's diverticulum in 1, and hereditary hemorrhagic telangiectasia in 1. Among the less common causes, special attention is drawn to pseudoxanthoma elasticum, von Willebrand's disease, diverticulosis of the colon, and the Mallory-Weiss syndrome. It was concluded that aspirin plays a definite part in precipitating gastroduodenal bleeding.

Patients with gastrointestinal bleeding of obscure origin should be investigated carefully. The personal history should be reviewed to find out if there had been any major emotional crisis in the few days preceding the bleeding. The patient's tendency to bleed and the possibility of recent medication with aspirin, cortisone, or phenylbutazone should be considered as a cause; the mode of onset of the bleeding should be recapitulated, with special thought to the possibility of Meckel's diverticulum. Splenomegaly is a constant accompaniment of portal hypertension and is masked only by obesity or ascites; in itself it raises the possibility of cirrhosis hepatis. The extent of further investigation will rest mainly on the clinical review of the case. Further barium meal, small intestine meal, and barium enema studies as well as liver function tests are necessary if findings of positive occult blood persist. A raised serum alkaline phosphatase value and dilated bile ducts may be found associated with an ampullary carcinoma. Laparotomy should be performed at the time of bleeding if positive findings persist. It is most important that the stomach should be opened and carefully inspected at the time of operation.

Compulsive Water Drinking. E. D. Barlow and H. E. de Wardener. Quart. J. Med. 28:235-258 (April) 1959 [London].

Severe polydipsia and polyuria without glycosuria may be due to (1) renal disease, including the renal complications of potassium deficiency and hypercalcemia, (2) compulsive water drinking, or (3) diabetes insipidus. In general, the diagnosis of renal disease is easy, and the principal diagnostic difficulty is to distinguish diabetes insipidus from compulsive water drinking. The authors describe the clinical features and physiological disturbances of 9 patients with compulsive water drinking, which is defined as an excessive consumption of fluid due to psychological disturbance. The ages of the 7 women and 2 men with compulsive water drinking ranged from 48 to 59 years, except for one woman who was 24 years old. Eight of the 9 patients had

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a history of previous psychological disorder, including hysteria, delusional hypochondriasis, and depression; the existing psychological disturbances ranged from delusions, depression, and agitation to frank hysterical behavior; one patient appeared normal. The consumption of water fluctuated irregularly from hour to hour or from day to day; in some patients there were remissions and relapses lasting several months or longer.

Compulsive water drinking was distinguished from diabetes insipidus by the clinical history and mental state of the patient, and by a fluid deprivation test performed after the kidney's ability to respond to vasopressin had been established. An estimation of plasma osmolality and the general effects produced by an injection of vasopressin tannate in oil were also found useful. The mean plasma osmolality in 8 compulsive water drinkers was significantly lower than normal; in 12 patients with diabetes insipidus it was significantly higher. The ability to concentrate urine after giving vasopressin intravenously varied considerably in 8 compulsive water drinkers, and in some it was severely impaired; this defect was unrelated to the urine output (5 to 20 liters in 24 hours) or the plasma osmolality. The urine concentration after fluid deprivation suggested that 6 patients were able to secrete antidiuretic hormone (ADH) normally, but that in 2 the ability to secrete ADH was impaired. After a remission of the compulsive water drinking, these 2 patients had a normal response to fluid deprivation. Vasopressin tannate in oil made most patients feel ill; in one it caused acute overhydration. In 4 patients the fluid intake returned to normal after electroconvulsive therapy or a period of continuous narcosis; the improvement was transient in 3 patients, but in the 4th it has lasted 2 years.

A diagnosis of compulsive water drinking is probable if, in the absence of renal disease or glycosuria, polydipsia and polyuria are intermittent, or if they are associated with other gross psychological disturbances, or if definite evidence of ADH secretion can be obtained. A diagnosis of diabetes insipidus is probable if, in addition to evidence of inability to secrete ADH, there are signs of a lesion in the neighborhood of the neurohypophysis, such as a calcified suprasellar cyst or a visual-field defect. The distinction between compulsive water drinking and diabetes insipidus is difficult in the presence of the following features: (1) persistent polydipsia and polyuria; (2) a normal mental state on superficial observation; and (3) when a test of neurohypophysial integrity suggests that the ability to secrete ADH is impaired, but there are no other signs of a lesion in the region of the neurohypophysis. In these circumstances the ability to secrete ADH should be investigated by another test, for if a normal response to a test of neurohypophysial integrity can be obtained by any means the diagnosis of diabetes insipidus is excluded. If it cannot be obtained, a diagnosis of diabetes insipidus is probable unless the plasma osmolality is below 275 milliosmoles per kilogram, or detailed observation and inquiry point to a definite psychological disorder, or treatment with vasopressin tannate in oil makes the patient ill.

SURGERY

The Cerebellar Astrocytomas: A Report on 98 Verified Cases. A. Gol and W. McKissock. J. Neurosurg. 16:287-298 (May) 1959 [Springfield, Ill.].

The authors report on 57 male and 41 female patients, between the ages of 1 and over 60 years, with astrocytoma of the brain. The average age of the 98 patients was 13 years. The tumor was confined to the cerebellum in 92 patients and to the roof of the 4th ventricle in 6. The latter 6 were included because of the similarity of behavior of the growth to that of the cerebellar tumors proper. Eighty of the 98 patients had a history of headaches and vomiting for many years, often made worse by stooping or straining. Exacerbations of symptoms may be separated by long periods of apparently good health. Symptoms occurring somewhat later were ataxia of the legs and arms, squint and diplopia, slurred speech, tilting of the head, stiffness of the neck, and attacks of unconsciousness or so-called cerebellar fits. The average length of history for all the patients was 16 months. Of the 92 patients with cerebellar tumors, 25 had tumors in the midline, 36 had tumors placed laterally, and 31 had lesions that involved both the vermis and one cerebellar hemisphere, i. e., median-lateral growths. The average age of the patients with median tumors was much lower than the average for the whole series, and the duration of symptoms was rather longer than the average for the entire series. The average age of the patients with lateral tumors was much higher than that of patients with midline tumors, but the duration of symptoms was shorter. An attempt was made to define clinical syndromes for the various situations of the tumor. The tumors were cystic in 84 patients. The histological picture was of low malignancy and did not appear to vary greatly with the site of the tumor.

Radical removal of the tumor was achieved in 63 patients, and in an additional 15 partial removal was accomplished, while in the remaining patients only biopsy or aspiration was considered advisable. Twenty-one patients (22%) died, and of those subjected to craniotomy, 17% died in the postoperative period. In this series the operative mortality among patients with tumors of the vermis was higher than among patients with other growths. The survival rate 5 years after complete removal of the tumor was 76%, and even partial removal of the tumor was followed by a 5-year survival rate of 56%.

Ventriculography with replacement of cerebrospinal fluid by air or iophendylate (Myodil) gave sufficient information to locate the lesion in 97% of the patients. It is suggested that the degree of ventricular dilatation present preoperatively may have a bearing on the immediate mortality rate.

Inflammatory Intervertebral Disc Disease as a Complication of the Operative Treatment of Lumbar Herniations. W. E. Stern and P. H. Crandall. J. Neurosurg. 16:261-276 (May) 1959 [Springfield, Ill.].

The authors report on 6 men and 3 women, between the ages of 28 and 64 years, who were operated on for the syndrome of herniation of the lumbar intervertebral disk and in whom inflammatory, or similarly progressive, disease of the intervertebral disk space and adjacent vertebral bodies occurred after surgical treatment of herniating nuclear disease of this space. In 3 of the 9 patients there developed frank postoperative suppuration of the wound, 1 had leptomeningitis, 1 had minimal drainage of the wound without demonstrable pathogenic agent, and the remaining 4 had no drainage of the wound but complained of disabling lumbar pain of weeks' or months' duration. Extensive radiologic evidence of destruction of the adjacent vertebral bodies and obliteration of the intervertebral space with occasional solid bony fusion was observed postoperatively in all 9 patients. The unusual severe disease process of the lumbar intervertebral disk in these patients thus was characterized by local pain and spasm in the back, variable degree of pain in the extremities, inconstant systemic reactions, and a delayed radiologic appearance of destruction and sclerosis. It occurred with and without immediate postoperative infection of the wound and suppuration.

That certain forms of this disease may occur without preceding operative manipulation is recognized. Bacterial agents, such as Staphylococcus pyogenes var. aureus and hemolytic streptococci, were responsible for the surgical complication in the patients with suppurative wounds and also in some of the other patients, thus presenting the commonest cause of this disease. Injurious mechanisms, other than bacterial agents, may, however, cause an identical clinical and roentgenologic aspect, not the least important of which may be a severe preoperative form of degenerative disease of the joint, which permits herniation of the disk to occur in the first place. The management of a patient with a postoperative soft-tissue abscess of the wound should include early and wide opening of the wound and drainage. Secondary closure of the wound at an appropriate time may shorten the convalescence materially. The treatment of the nonsuppurating, chronic form of the syndrome is conservative; the morbidity is prolonged, and during the symptomatic period of lumbar pain and spasm, bed rest or activity restricted to tolerance is the most satisfactory recommendation. The ultimate prognosis is good.

Bilateral Mammary Carcinoma: Clinical Contribution. F. De Bernardis and A. E. Vaccato. Acta. chir. ital. 15:163-178 (March-April) 1959 (In Italian) [Padua, Italy].

The authors studied the interdependence of the primary and secondary lesions of bilateral mammary carcinoma in 18 patients, aged between 30 and 67 years. Simultaneous appearance of histologically similar varieties of tumor developed in 2 patients. There was a short interval, from 35 to 65 days, between the appearance of the primary and the secondary lesion in 3 patients with histologically different tumors. The interval varied from 1 to 2 years in 4 patients with histologically similar tumors. A still longer interval took place in 9 patients, 6 of whom had histologically similar varieties of tumor. It seems that the hormonal imbalance of the menopause was the etiological factor of the double lesion in 11 patients (61%). The histological varieties of the primary tumor, in decreasing order of sequence, were adenocarcinoma, scirrhous carcinoma, hard carcinoma, fibrocystic disease of the breast with degeneration, and sarcoma. The histological varieties of the secondary tumor, in decreasing order of sequence, were fibrocystic disease of the breast with degeneration, scirrhous carcinoma, hard carcinoma, and adenocarcinoma. Halsted's operation was performed in all but 2 inoperable instances of the primary tumor. Radical mastectomy was performed on 8 patients with secondary tumor (50%). Roentgenotherapy combined with biochemical therapy, which consisted of the administration of 250 mg. of testosterone a week, was given to all patients. The results were unsatisfactory, because only 5 patients (22%) survived during a long-term period of observation.

Chemodectoma of the Ganglion Nodosum of the Vagus Nerve: Critical Revision and Clinicohistological Contribution to the Study of the Nonchromaffin Intravagal Paragangliomas. F. Brunetti and V. Mollica. Cancro 11:521-538 (no. 6) 1958 (In Italian) [Turin, Italy].

A painless mass in the neck, situated posterior to the angle of the mandible, appeared 3 years before hospitalization in a woman, 18 years of age. On admission, the tumor was the size of a small orange. At operation, a vascular, encapsuled tumor, from 3 to 4 cm. in maximal dimension, partly lobar, and intimately associated and in continuity with the vagus nerve, was removed. The excised mass was diagnosed as a chemodectoma of the ganglion nodosum of the vagus nerve. The presence of a marked glosso-laryngo-scapulo-velar hemiplegia,

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which was observed after the effect of the anesthetic had worn off, caused the patient difficulty in breathing; therefore, an emergency tracheotomy was performed the following night, followed by a plastic tracheostomy after the tracheal cannula had been removed. The patient was in good general health and free from symptoms in the neck for 3 years after the operation, although the hemiplegia persisted on the right side. Microscopic examination of the excised mass revealed that the tumor had a pseudoalveolar structure with osseous tissue in its various sections. Intermediate osteoid structures, revealing phases in the transformation of the neoplastic cells until final formation of the osseous tissue, were also demonstrated.

Isolated Infundibular Stenosis. S. G. Blount Jr., P. S. Vigoda and H. Swan. Am. Heart J. 57:684-700 (May) 1959 [St. Louis].

While some observers consider isolated infundibular stenosis (subvalvular pulmonic stenosis with intact ventricular septum) a not uncommon congenital heart lesion, others consider it a very rare congenital lesion. The authors present the histories of 3 patients with well-documented infundibular stenosis, with preoperative and postoperative catheterization data. The first patient was a 21-year-old woman, the second a 20-year-old youth, and the third a 9-year-old boy. The 3 patients were operated on under hypothermia. Symptomatically, they all are much improved; they feel better, and their exercise tolerance is increased. On physical examination, the thrill has disappeared in all the patients, and the murmur has decreased in intensity. Postoperative catheterization revealed that in 2 patients (patients 1 and 3) the pressure gradient was completely abolished. In the second patient the pressure gradient was reduced, being 71 mm. Hg preoperatively and 36 mm. Hg postoperatively.

The authors regard it as interesting that postoperative catheterization revealed pulmonary hypertension in the third patient. This boy also showed a diastolic shock in the pulmonary area on palpation, and a loud pulmonic component to the second sound. This phenomenon has been noted in patients following valvulotomy for valvular pulmonic stenosis. The boy had an elevated pulmonary arterial pressure prior to surgery, and when the obstructing lesion was removed, there was a further rise in the pressure level. The thought that he had multiple small pulmonary emboli or thrombosis of pulmonary arterioles has been considered. The electrocardiograms of 2 patients showed a significant diminution in the degree of right ventricular hypertrophy, while it was unchanged in the third patient. It is of interest that this patient, who had a drop in right ventricular pressure of 90 mm. Hg following surgery, has shown no change in his electrocardiogram one and one-half years after the operation.

The authors found that at the University of Colorado Medical Center in Denver, there were 4 patients with isolated infundibular stenosis among 138 with pulmonary stenosis, an incidence of about 3%. Auscultation offers the most reliable aid in differentiating infundibular from pulmonary valvular stenosis. In infundibular stenosis the murmur and thrill are of maximum intensity in the second to third left intercostal spaces parasternally, or lower, and the murmur is always louder in the third left intercostal space than in the first left intercostal space. The quality of the murmur is considered to be more rasping in the infundibular variety. Cardiac catheterization is diagnostic if an infundibular-chamber pressure curve can be demonstrated. In its absence, the finding of a transition zone between the pulmonary arterial pressure curve and the right ventricular pressure curve at a point much below the usual site of the valve should make one suspect infundibular stenosis. It is important to differentiate preoperatively an isolated infundibular stenosis with a patent foramen ovale from the tetralogy of Fallot, because the surgical procedures and the risks involved are quite different. An infundibular stenosis can be successfully corrected by surgery with but a slightly higher risk than that in valvular stenosis.

Adamantinoma of the Jaws: A Clinicopathologic Study of 101 Histologically Proved Cases. J. K. Masson, J. R. McDonald and F. A. Figi. Plast. & Reconstruct. Surg. 23:510-525 (May) 1959 [Baltimore].

The records of 101 patients with adamantinoma of the jaws were studied at the Mayo Clinic. Forty-six of the patients were males, and 55 were females, ranging in age from 9 to 82 years; the highest incidence was in those between the ages of 50 and 59 years. The tumors were classified according to histological picture into 4 main groups: plexiform (67); squamous (24); glandular (8); and sarcoma-like (2). An attempt was made to correlate the clinical course with the histological picture. It was not possible to establish which of these histological types was more malignant. All the tumors were capable of recurrence, and the number of recurrent lesions was directly in proportion to the number of tumors in each group. Metastasis occurred in one patient with an adamantinoma in which the squamous elements predominated; the secondary tumor involved a lymph node in the upper cervical region. The number of patients with recurrent adamantinoma at the time of admission (72%) was considerably higher in this series than in any other group reported.

Adamantinoma is a slowly growing, epithelial tumor which most frequently involves the jaws, particularly the lower jaw. It occurs most often in middle life and is observed slightly more frequently

in women than in men. It recurs after incomplete removal in alomst 100% of the cases and is capable of invading soft tissues and bone. The question whether it is malignant is still debated. Only one tumor in this series proved its malignant characteristics by distant metastasis to a cervical lymph node. Generally the lesion is benign, with a characteristic tendency to recur.

Pulmonary Resection for Metastatic Tumors. H. C. Habein Jr., O. T. Clagett and J. R. McDonald. A. M. A. Arch. Surg. 78:716-723 (May) 1959 [Chicago].

This study is an extension and continuation of 2 previous studies on the results of pulmonary resection carried out at the Mayo Clinic in an attempt to eradicate metastatic tumors of the lungs. By the end of 1956, a total of 96 patients had undergone pulmonary resection for metastatic malignant tumors, the first procedure of this nature having been carried out at the clinic in 1941. (The series does not include patients on whom only biopsy of the pulmonary lesion was performed.) The patients ranged in age from 6 to 73 years, the greatest number being between 40 and 60. Follow-up data are complete in 93 of the 96 cases. Many of these patients have been seen at regular intervals at the clinic. In other instances, follow-up letters were answered by the patient, his relatives, or the home physician. The interval between treatment of the primary tumor and resection of the metastatic pulmonary lesion varied from zero to 22½ years. The primary operation in all instances was curative in objective. In 4 patients the pulmonary operation was carried out prior to removal of the primary tumor.

The 93 lesions included 73 carcinomas, represented most frequently by tumors of the colon, rectum, and breast, but including such lesions as melanoma, teratoma of the testis, hypernephroma, and squamous-cell carcinoma of the cervix. One patient had 2 separate primary carcinomas of the breast. The remaining 20 primary lesions were classified as sarcoma, osteogenic sarcoma, and fibrosarcoma. The sex incidence was about equally divided, contrasting with the preponderance of males in primary bronchogenic carcinoma. The usual metastatic tumor in this group was characterized by a peripheral location, distinct margins, and homogeneous density. The diameter varied from 1 to 7 cm. The great majority of these patients had no demonstrable pulmonary lesions at the time of operation on their primary tumors. In only 10 instances was pulmonary metastasis known to have been present at the time of the primary operation.

Lobectomy was performed on 60 patients, pneumonectomy on 24, segmental resection on 7, and local or wedge excision on 5. In only 2 patients was it necessary to resect a portion of the thoracic wall or parietal pleura in treating the pulmonary tumor. Only one death occurred in the postoperative period. Of the 93 patients who could be traced, 16 were living without evidence of recurrence 3 or more years after the pulmonary operation. Although 44 patients died less than 2 years after the metastatic pulmonary lesion was removed, 12 patients lived 2 or more years before succumbing to the disease. Another 6 patients were alive despite recurrent malignant tumors 2 or more years after pulmonary resection. Although many of the results in this study were disappointing, some remarkable "cures" were obtained, and several patients experienced considerable palliation. The authors feel that resection is indicated for pulmonary metastasis in carefully selected cases. Other conditions being favorable, exploration should be considered seriously for an indeterminate pulmonary lesion in a patient with a previous history of malignancy.

Spontaneous Hemorrhagic Rupture of the Kidney Associated with Periarteritis Nodosa. I. Mandelbaum and L. R. Radigan. Surgery 45:787-795 (May) 1959 [St. Louis].

Rupture of the kidney with retroperitoneal hemorrhage is usually a sequel of external trauma, but there have also been a few cases of spontaneous rupture without a history of trauma. The authors present 2 patients with periarteritis nodosa and renal rupture with massive hemorrhage, who were studied or treated at the Indiana University Medical Center in Indianapolis during the past 5 years. The first patient was a 36-year-old man who had been known to have hypertension for 10 years with severe acceleration of the hypertension for 1 year. He entered the hospital with left flank pain of sudden onset and evidence of massive retroperitoneal hemorrhage and shock. There was no antecedent trauma. A rupture of the lower pole of the left kidney with hemorrhage into the retroperitoneal space was discovered at operation, and the laceration was repaired. The patient recovered only to succumb 3 months later with evidence of severe hypertension and mental confusion. Renal biopsy at operation showed arterial and arteriolar nephrosclerosis. Skin and muscle biopsy revealed nonspecific vasculitis. The final diagnosis at postmortem examination was periarteritis nodosa involving many organs.

The second patient was a 32-year-old farmer, who had a 4-month history of severe hypertension for which he was being studied and treated. Pain suddenly developed in the left flank, and the man died 2 hours later. There was no previous history of trauma, and he had been constantly observed in the hospital for 2 weeks. Postmortem examination revealed a local rupture of the left kidney with massive retroperitoneal hemorrhage. An artery of moderate size at the corticomedullary junction with

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fibrinoid necrosis of the wall communicated with the retroperitoneal area. There was focal fibrinoid change and inflammation of the afferent glomerular arterioles and small arteries of the kidneys. Fibrinoid changes with inflammation, characteristic of periarteritis nodosa, were noted in many small and medium-sized arteries in many organs throughout the body.

The authors cite literature on 3 other patients in whom ruptured kidney was associated with periarteritis nodosa. Treatment should aim at stopping the hemorrhage and saving as much renal tissue as possible. Such efforts may avert death from exsanguination, but cannot be expected to alter the course of the underlying disease. Periarteritis nodosa is one of a group of so-called collagen diseases. This classification merely denotes the common findings of connective tissue alterations characterized by fibrinoid necrosis. In most pathological studies, the kidney has been the site of the most profound morphologic changes.

Desmoid Tumor of the Abdominal Wall: Use of Prednisone to Prevent Recurrence in a Child. T. C. Panos and E. J. Poth. Surgery 45:777-779 (May) 1959 [St. Louis].

The authors define desmoid tumor as a benign, unencapsulated, fibrous neoplasm which may grow to a large size and/or cause extensive local infiltration and destruction of adjacent striated muscles; it may also become fixed to surrounding structures, such as bone. Because of these characteristics, wide excision has become the operation of choice. The danger of recurrence is great and ensues rapidly after incomplete removal. Subsequent removal may be difficult or impossible and may require drastic general and plastic surgical assault. Recurrence appears to be more likely in children than in adults, and at least one death has been reported as a result of repeated recurrences. The authors present the history of a girl who was first admitted to the University of Texas Hospitals in Galveston on July 6, 1954, at the age of 22 months with the chief complaint of "bladder tumor." Three days prior to that date, the mother had noted a firm, nontender mass in the lower midabdomen. A smooth, firm mass was situated just above the pubis and to the right of the midline. The impression was neoplasm arising in the abdominal wall.

At surgery, the tumor was found to involve the rectus muscle and posterior sheath. The thickened tissues extended down to the symphysis, and they were excised close to the bone. Additional pieces of tissue were taken from the edges and were studied microscopically. The superior section showed additional tumor. Additional midline structures in the rectus sheath were excised until no tumor was identifiable. The patient tolerated the procedure well. Microscopic section of the tumor showed well-differentiated spindle-shaped cells separated by a large amount of fibrocollagenous tissue. The pathological diagnosis was desmoid tumor of the abdominal wall. The patient was discharged on July 24, 1954. Recurrence was noted in the operative area on Dec. 20, 1955. Respiratory infection delayed further surgical treatment until Jan. 9, 1956, at which time there was a mass, 4 by 6 cm., in the area of the old scar. The tissues of the lower abdomen up to and including the umbilicus were thickened and indurated. The previous scar was outlined and excised down to the subcutaneous tissue. Desmoid tumor tissue was present in both umbilical and left-angle tissues. The excision was extended in these regions. The patient withstood the procedure well. Microscopic section revealed the histological pattern of the tumor to be essentially identical with that from the previous operation.

Evidence of local recurrence and extension was detected 2 months later, in March, 1956. Further surgical management was considered impossible. The pronounced antifibroblastic activity of the glucocorticoid hormones suggested a therapeutic trial with prednisone (Meticorten). Accordingly, the patient was placed on the following Meticorten regimen with appropriate ancillary precautionary measures: 10 mg. every 6 hours for 7 days; 7.5 mg. every 6 hours for 4 days; 5 mg. every 6 hours for 6 days; 17.5 mg. a day for one week, then gradual decrements of 2.5 mg. until a daily dosage of 5 mg. was reached. Response to this therapy was spectacular, the nodule having disappeared within 3 weeks. The lower abdominal wall became progressively softer and more pliable until by May 2, 1956, there was no thickening or induration. The child continued to thrive on a daily maintenance dose of 5 mg. of Meticorten. Except for a slight "Cushingoid" appearance, steroid therapy caused no complications. These encouraging results have prompted recommendation of further trial of this type of therapy in patients in whom surgical management of desmoid tumor is not feasible.

Psychiatric Observations on Fifty Postgastrectomy Patients. P. C. Rond. Surgery 45:729-737 (May) 1959 [St. Louis].

A duodenal ulcer is conceded by many internists and psychiatrists to be a psychosomatic illness, the physical expression of anxiety deflected into a body organ with the resultant development of physical disease. A random sample of 105 patients who had undergone gastrectomy were called in by the surgeon for postoperative follow-up studies. The surgeon examined all 105 patients, and 50 of them were subjected to a psychiatric evaluation by the author. Prior to a 60-minute interview, the patient was informed that the examiner was a psychiatrist and that he was interested in the emotional aspects

of peptic ulcer. The operation performed on all the patients was a Billroth I procedure, with a bilateral vagotomy. In this procedure 50 to 60% of the stomach is removed, and a new attachment is made to the small intestine. None of the patients interviewed had a recurrence.

The group was made up of 42 men and 8 women who ranged in age from the 30's to the 70's and who came from all levels of the socioeconomic scale. All the patients had had duodenal ulcers, which had produced severe pain, hemorrhage, or obstruction. All were operated on by the same surgeon. At least one year had passed since operation, and most of the patients were in the more than 2-year range. Suggestive questioning was avoided during the interviews; rather the patients were encouraged to talk about themselves, so that spontaneous material might be forthcoming which would be a true expression of their thoughts and feelings. Subjective experiences and the part they played in their lives were discussed and evaluated. The patients were divided into 4 groups, with only 1 group (6 patients) expressing dissatisfaction with the operative results. The other 3 groups (44 patients) expressed satisfaction with the operative results, even though some had complaints.

The author concludes that emotional factors play a vital part in the duodenal ulcer patient's symptoms before and after operation. They play a role in the aggravation of ulcer symptoms, in the production of the dumping syndrome, in the complaint of pain postoperatively, and in the bringing of the patient to surgery. When the surgical procedure is carried out, the results are very closely tied to the state of emotional balance present in the patient at the time. If the ulcer is the primary stress factor, in a stable personality its removal leads to excellent results postoperatively. If, however, the ulcer is associated with an emotionally unstable personality, nothing but poor results can be expected. Finally, where the personality balance is not completely inadequate, and the ulcer is not the chief source of stress, varied results occur. This is the group in which predictability varies. Here one finds the postgastrectomy syndrome, with or without complaint. In this group one also finds the postgastrectomy syndrome clearing, with later emotional changes. More intensive psychiatric study is needed of the postgastrectomy, dumping, or postprandial syndrome in relationship to emotional factors.

Effect of Triethylenethiophosphoramide (Thio-TEPA) upon Healing of Abdominal Wounds. S. M. Farhat, D. M. Miller and M. M. Musselman. A. M. A. Arch. Surg. 78:729-731 (May) 1959 [Chicago].

Triethylenethiophosphoramide (thio-TEPA) and mechlorethamine (nitrogen mustard) are used at the time of operation for cancer to discourage the local and distant implantation of cancer cells in the body. If these cytotoxic drugs are capable of destroying the malignant cells, it is logical to question whether they might also affect the young and proliferating cells of a healing wound. In a previous report the authors showed experimentally that mechlorethamine interfered with the healing of wounds and reduced their tensile strength; it also caused weight loss in animals. The authors were unable, however, to determine whether reduction of tensile strength was a direct result of mechlorethamine on the healing wound or secondary to malnutrition (as manifested by loss of weight). In the present study the effect of thio-TEPA on the healing of abdominal wounds in rats was determined, and it was found that thio-TEPA did not interfere with the healing of such wounds. No interference with or alteration in the fibroblastic proliferation or collagen deposition could be demonstrated. From these findings the authors conclude that the administration of thio-TEPA has no effect on the rate of wound healing and does not reduce the tensile strength of wounds.

NEUROLOGY & PSYCHIATRY

Penicillin Treatment of General Paresis (Dementia Paralytica): Results of Treatment in 1,086 Patients, the Majority of Whom Were Followed for More Than Five Years. R. D. Hahn, B. Webster, G. Weickhardt and others. A. M. A. Arch. Neurol. & Psychiat. 81:557-590 (May) 1959 [Chicago].

The authors present a cooperative report of the clinical, spinal fluid, and serologic findings in 1,086 patients with general paresis (dementia paralytica), who were treated with penicillin with or without fever therapy at 8 different hospitals. Only a few of the patients had received any treatment for early syphilis, and in none of them had this treatment included administration of penicillin. Treatment for general paresis consisted of administration of aqueous penicillin in 85% of the patients, procaine penicillin in 12%, and penicillin in oil and wax or mixed types in the remaining 3%. Ninety-seven per cent of the patients received more than 2.4 million units, and 58% received more than 6 million units. Of the 1,086 patients, 457 were treated with fever and penicillin and 629 were treated with penicillin alone. Although the minimal effective dose of penicillin is unknown, the results obtained in these patients permit the pragmatically important conclusion that a dose of 6 million units is ample.

The effects of treatment on the individual symptoms and signs of general paresis, such as disorientation, convulsions, tremors, and incontinence, were, in general, strikingly beneficent. In most of the patients, though, impairments of speech, insight, calculation, judgment, and general information did not entirely disappear. Follow-up of a significant number of patients through the 6th or 7th year after treatment revealed that progression

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and death due to neurosyphilis occurred almost altogether in patients with severe pretreatment psychoses. Post-treatment psychiatric hospitalization was directly proportional to, and clinical improvement and rehabilitation for work were inversely proportional to, the severity of pretreatment psychosis. Type of psychosis was of less importance than was severity of psychosis. The shorter the duration of paretic psychosis at time of treatment, the more frequent was clinical improvement and rehabilitation for work. The presence at time of treatment of incontinence, of inability to dress self and perform other simple acts of personal toilet, and, to a less extent, of convulsions afforded a particularly poor prognosis for longevity. Work status at time of treatment was of great prognostic importance, since 82% of those able to work before treatment continued to be able to work; of those unable to work before treatment, 56% were rehabilitated for work; and of those institutionalized before treatment, 33% were rehabilitated. Or perhaps equal prognostic significance was the length of time which had elapsed since the patient had been able to work at his usual occupational level. Age within the limits of 30 to 59 years, race, and sex were relatively unimportant factors in the prognosis of general paresis.

The Herxheimer reaction, notably exacerbation of the paretic psychosis or convulsive seizures occurring within a few days after the initiation of treatment, was observed more frequently in the presence than in the absence of spinal fluid pleocytosis. Pretreatment sedation and often the use of anticonvulsants are advisable. The Herxheimer reaction did not cause long-term damage in general paresis. Pretreatment pleocytosis indicates an active inflammatory process more susceptible of improvement by treatment, but in a minority of patients leaving behind sufficient brain damage to nullify any real clinical effect. The absence of pleocytosis indicates a relatively static process but, at the same time, one less likely to progress. Pretreatment spinal fluid protein levels are of less prognostic import. Persistent cell counts of 11 or more were not usually observed after penicillin treatment. Clinical progression did, however, occur significantly more frequently with persistent cell counts of 5 to 10 than with cell counts of 4 or less. Persistent spinal fluid protein elevations were relatively frequent, but of no prognostic import.

The trend in recent years in the United States has been toward the treatment of general paresis with penicillin alone. The possible additive effects of fever therapy are not sufficient to justify its use in any significant number of patients. The early diagnosis and prompt penicillin treatment of incipient paresis will result in clinical remission and ability to work in more than 80% of patients and will practically prevent all deaths from neurosyphilis. Absence of clinical improvement, persistently abnormal spinal fluid protein level, or persistently positive Wassermann reaction of spinal fluid are not indications for retreatment. Retreatment with penicillin is indicated under the following circumstances: an initial course of less than 6 million units, temporary clinical improvement after an initial course with subsequent clinical progression, or spinal fluid count of 5 or more after the first post-treatment year. The essentially identical probability of death in patients who received one course of treatment and in patients who received more than one is strong evidence against the value of routinely repeated courses of penicillin in the treatment of general paresis.

Cerebrospinal-Fluid Culture in Multiple Sclerosis. H. Mavor, F. W. Gallagher and G. A. Schumacher. New England J. Med. 260:860-863 (April 23) 1959 [Boston].

The authors collected cerebrospinal fluid specimens for cultivation from 26 patients, 12 of whom had multiple sclerosis and 14 had a variety of other, predominantly neurological, disorders. The cultures of 6 of the 26 specimens were contaminated with gram-positive organisms and were removed from consideration. All the cultures of the remaining 20 specimens (9 from patients with multiple sclerosis and 11 from control patients) remained sterile and were considered satisfactory. The cultures from these 20 specimens remained negative for evidence of spirochetes during periods of incubation of at least 30 days. The failure to obtain growth of spirochetes in cultures of cerebrospinal fluid specimens from patients with multiple sclerosis is at striking variance with a previous report of positive cultures in 78% of such cases.

Herpetic Osteoporosis. F. Layani, L. Durupt and J. Paquet. Semaine hôp. Paris 35:1273-1281 (April 12) 1959 (In French) [Paris].

The rarity of osteoporosis as a complication of herpes zoster lends interest to the report of a new case which occurred in a 65-year-old woman whose illness began in July, 1957. The eruption, which was cervicobrachial in distribution (C-3, C-4, C-5, C-6), was accompanied by burning pains that subsided little by little. Concurrently, the patient complained of progressive functional incapacity of the arm and neck. A second eruption affecting the same regions as the first appeared one month later and was treated with anti-inflammatory roentgenotherapy to the neck. The recurrence of the pain, aggravation of the functional incapacity, appearance of edema in the hand, and muscular weakening of the arm then led the patient to seek further advice. Her arm was held in a typically antalgic attitude on examination, with the elbow pressed against her side; her head was bent to the right; and attempts to move the neck, shoulder, and elbow were intensely

painful. Evidences of the herpetic eruption were visible on the skin. Roentgenographic examination revealed extensive osteoporosis affecting the cervical spine, the scapular girdle and the right arm, the carpal block, and the bones of the right hand. Symmetrical but less pronounced osteoporotic lesions were also found on the opposite side. Biological studies revealed no abnormalities. Vigorous physical therapy, consisting of active massage, heat, and functional reeducation, was immediately instituted in association with the administration of ganglioplegics. This treatment proved effective, and by the end of 5 weeks the pain had practically disappeared; hypersudation and edema were regressing, and the mobility of the affected joints had increased to a notable degree. Progressive improvement in the patient's condition continued, but more than a year of treatment was needed before full recovery with almost complete remineralization of the skeleton was secured.

The pain of herpes usually disappears with the subsidence of sympathetic irritation. The irritation persists, however, in certain predisposed patients, causing severe postherpetic pain and leading at times to vasomotor reactions that explain the neurotrophic syndrome with its accompanying osteoporosis. The close resemblance between this syndrome and post-traumatic algesic osteoporosis seems to show that irritative injury to the sympathetic nerve, whether it comes from a fracture or from a herpetic infection, may in certain favorable conditions produce the same local vasomotor reactions. Herpetic osteoporosis thus appears to be a simple variant of the post-traumatic osteoporosis of sympathetic origin described by Leriche. Treatment, then, must be designed (1) to combat vasomotor disturbances by modifying the local circulatory conditions through direct action on the sympathetic nerve, (2) to counteract the painful stiffening of the joints and the muscular atrophy by well-managed physical therapy, and (3) to modify as far as possible the neurovegetative terrain and possibly the neuroendocrine constitution.

The Contribution of Laboratory Examinations to the Diagnosis of Poliomyelitis (Parallel Clinical and Biological Studies in 311 Cases). S. Thieffry, M. Arthuis, C. Martin and others. Semaine hôp. Paris 35:1343-1349 (April 18) 1959 (In French) [Paris].

The authors report on 311 children in whom a clinical diagnosis of poliomyelitis was made at the Children's Hospital in Paris and who were treated in close cooperation with the virological laboratory of the French Association for the Study and Care of Children with Poliomyelitis in Paris. A comparison of the criteria for the clinical diagnosis with those for the virological diagnosis of poliomyelitis in its usual form, made at the sick bed, justifies the following conclusions: 1. In the course of the first 10 days of the disease, the chances of detecting the poliomyelitis virus in the feces of the patient are at present 99%; this ratio diminishes after the 10th day of the disease. 2. From the first days of the disease, the neutralizing homotype antibodies are present in the patients' serums; the antibody titer is variable. 3. Under the usual conditions of obtaining the serum specimens, it is not easy to determine the increase in the homotype antibody titer on successive examinations.

By applying these findings to the problem of confirming the clinical diagnosis with the aid of the laboratory findings, one is justified to assume that, according to today's knowledge, the detection of the virus and of the homotype antibody at an increasing rate during the first days of the disease constitutes the best proof of the reality of poliomyelitis. In the course of a disease which could raise the suspicion of poliomyelitis, the absence of the virus, searched for under favorable conditions, is an indication of high value, particularly when the parallel search for neutralizing antibodies has yielded negative results on successive examinations. Such a negative result represents an argument in the differential diagnosis of the disease. On the contrary, the presence of the virus in the feces does not imply by itself alone that the disease is poliomyelitis. The presence of antibodies also is not of absolute significance. Virological studies appear to be an essential prerequisite for all attempts to extend the frame of poliomyelitis, but they are not indispensable for the diagnosis of the usual forms of poliomyelitis.

Nervous Complications Associated With Vaccination Against Poliomyelitis. F. Graser and G. Fortong. Monatsschr. Kinderh. 107:227-230 (April) 1959 (In German) [Berlin].

The authors report on 5 boys, between the ages of 1½ and 12 years, and on a 2-year-old girl, in whom flaccid pareses, spasms, obnubilation, and disturbances of swallowing and respiration were observed, in addition to febrile reactions, sore throat, rash, and bouts of eczema, after vaccination against poliomyelitis. These nervous manifestations occurred in the course of one week after the first or the second injection of Salk's vaccine. In the first 5 of the 6 children the nervous complications were transitory, associated with a rash and with normal cerebrospinal fluid findings. Neither poliomyelitis virus nor parapoliomyelitis virus was found in the feces and the cerebrospinal fluid. The nervous complications were, therefore, considered to be radicular, myelitic, and encephalitic reactions of an allergic type.

In the 6th patient, a 2-year-old boy, extensive pareses of both lower extremities associated with high fever occurred on the 6th day after the first

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injection of the vaccine. On admission, the patient was somnolent and was completely paralyzed with the exception of the muscles of the face and the head rotator muscles. Respiration was superficial, and cough was weak. A slight increase in cells with 84 leukocytes per cubic millimeter was found in the cerebrospinal fluid. In the course of the next 2 days the condition of the patient deteriorated; he could not turn his head, there was pronounced respiratory insufficiency and difficulty of swallowing, high fever, and obnubilation. Treatment with cardiovascular agents and antibiotics was instituted. The temperature was restored to normal, respiration improved, and responsiveness of the mind was restored. The flaccid paralysis subsided slowly, and 10 weeks after the onset of the encephalomyelitic process there still seemed to be danger of permanent damage. Then the pareses disappeared, except for mild weakness in the legs and feet. Poliomyelitis or parapoliomyelitis virus was not found in the feces and cerebrospinal fluid, and, therefore, a poliomyelitis infection could not be definitely considered as the cause of the severe pareses, and an allergic vaccinal complication could not be entirely excluded. These observations suggest that disturbances of the central nervous system, the course of which may not always be mild, should be expected after poliomyelitis vaccination, in addition to local reactions, disturbances of the general condition, anaphylactic shock, urticaria, sore throat, and gastrointestinal disturbances.

Immuno-Epidemiologic Study of Two Infant Nursery-Community Groups Infected by Viruses of Poliomyelitis. J. Zourbas and V. Drouhet. Semaine hôp. Paris 35:1356-1362 (April 18) 1959 (In French) [Paris].

The authors report on 2 epidemics of poliomyelitis occurring in 2 day nurseries for infants in the Seine province of France in 1957. Of 28 infants with poliomyelitis in nursery A, type 2 virus of poliomyelitis was detected either in the pharynx or in the feces of 26 patients. Of 41 infants with poliomyelitis in nursery B, type 1 virus of poliomyelitis was detected in 39 patients. The virus was noted in the pharynx of 60% of the patients and in the feces of 94% of the patients. The period of the elimination of the virus in the feces exceeded the 46 days of the study of these patients and was longer than the period for which the patients carried the virus in the pharynx. These observations suggest that infants in a nursery community react to the poliomyelitis virus infection with an incontestable epidemiologic unity. This unity was noted again in the course of systematic serologic studies which revealed the presence or appearance of homotype antibodies in all but 2 of the infants studied; those 2 were very young, and in patients of this age the homologous antibodies are present only in a dilution of 1:2. In contrast to these findings, specimens obtained from the adult personnel of the nurseries were all negative concerning the pharynx, and concerning the feces they were positive only in 2 of the 10 persons employed with nursery A.

PEDIATRICS

Two Instances of a Peculiar Combination of Malformations: Asplenia, Congenital Heart Defect, and "Situs Inversus" Below the Diaphragm. F. Favini-Sacerdoti and C. Nadin. Acta paediat. latina 12:51-65 (Jan.-Feb.) 1959 (In Italian) [Reggio Emilia, Italy].

The authors describe cases of asplenia associated with congenital defect of the heart and partial situs inversus below the diaphragm in 2 infants, one of whom died on the 6th day of life and the other after 2 months of life. On admission, one infant had diffuse cyanosis, dyspnea, and asthenia; the other had diffuse cyanosis, polypnea, and diffuse edema. The following malformations were observed on autopsy: absence of spleen, considerable defects of interatrial and interventricular septums, presence of a common ostium atrioventriculare, and partial transposition of the stomach and pancreas. In addition to these common malformations, atresia of the trunk of the pulmonary artery with transposition of the large arteries, stenosis of the lower part of the esophagus, and a common mesentery were observed in one infant. A common arterial trunk, persistence of the left inferior vena cava, abnormal outlet of pulmonary venae into the superior vena cava, and abnormal pulmonary lobes were present in the other infant. The authors believe that the dominant feature of this syndrome is not cardiopathy or asplenia but loss of visceral symmetry.

The Effect of Large Doses of Prednisone on Acute Rheumatic Fever: Observations on the Treatment of Seventeen Patients with Carditis with a Two-Year Follow-Up. C. Ferencz, M. Markowitz and J. J. Bunim. A. M. A. J. Dis. Child. 97:561-570 (May) 1959 [Chicago].

The authors report on 8 boys and 9 girls, between the ages of 5 and 13 years, with acute rheumatic fever of less than one month's duration, who were treated with large doses of prednisone for an average period of 14 weeks at 3 hospitals in Baltimore. Fourteen of the 17 patients had their first attack of rheumatic fever; mild carditis was present in 5 patients, and moderately severe carditis in 12. Prednisone was administered in doses of 50 to 75 mg., given in 4 divided doses, each day for 9 weeks. The administration was then tapered over a period of 4 to 6 weeks. The average total dose of the drug was 4.8 Gm. Prednisone produced a satisfactory response in fever and joint manifestations

in all the patients. In general, the anti-inflammatory and antirheumatic effects of prednisone in the doses administered were comparable to those noted in previous studies with 200 to 300 mg. of cortisone per day. The use of a relatively long course of prednisone did not prevent a return of rheumatic manifestation when administration of the drug was terminated. Recurrences occurred in 14 patients but subsided without treatment in all instances. Marked signs of hyperadrenocorticism occurred in all the children. Edema or hypopotassemia did not develop in any of the patients on a normal diet, without the addition of potassium. Hypotension was the most serious toxic effect observed and was the cause of a convulsion in one patient.

At the end of a 2-year follow-up period 4 of the 17 patients had evidence of rheumatic heart disease. Two additional patients had questionable heart disease. While no conclusions can be drawn from this small uncontrolled study of the efficacy of prednisone in reducing the incidence of heart disease, these results indicate that the use of large doses of this steroid over a prolonged period in children early in their attack of rheumatic fever does not prevent cardiac sequelae in all patients.

Segmental Atelectasis in Children with Primary Tuberculosis. S. Frostad. Am. Rev. Tuberc. 79:597-605 (May) 1959 [New York].

The author performed 270 bronchoscopic examinations on 90 children with segmental atelectasis after primary tuberculosis. Bronchial stenosis as a result of lymph node compression was found in 61 children (67.8%), and lymph node perforation of the bronchial tree in 25 (27.8%). In only one child were the findings completely negative on bronchoscopic examination. Both the atelectasis and the complications, such as lymph node perforation, were more frequently observed on the right side. Lymph node perforation was found more often in children younger than those belonging to the school-age group, and more frequently in boys than in girls. Lymph node perforations in children often appeared without symptoms (few children had any symptoms at all), but coincident with these perforations simultaneous clearing of the atelectatic zones was observed in the lungs of the children from whom chest roentgenograms were obtained. This finding not infrequently led to the correct diagnosis—the lymph node perforation—being verified at the next bronchoscopic examination. The lymph node perforations appeared despite antituberculous chemotherapy, and even 12 to 14 months of chemotherapy did not prevent a lymph node perforation.

Bronchographic examinations of 33 children at the end of the therapy period revealed abnormalities in 27. A total of 31 segments were resected in 15 children with segmental atelectasis. Signs of progressive tuberculosis, in addition to bronchiectasis, atelectasis, and lung fibrosis, were observed in the resected segments of 12 of these patients. In contrast to other reports, it was found that the course of the disease in a patient who had had an intimate infectious contact with a tuberculous mother was not more serious than in contacts with other sources of infection.

Contributions to Knowledge of Boeck's Disease in Childhood. H. Doose and C. Berderli. Monatsschr. Kinderh. 107:218-227 (April) 1959 (In German) [Berlin].

The authors report on a 9-year-old girl and on an 11-year-old boy with sarcoidosis, who were admitted to the pediatric clinic of the University in Kiel, Germany. Tertiary pulmonary changes, increased size of the spleen with splenogenic anemia, hypercalcemia with deposits of calcium in the spleen and kidney, and nephrocalcinosis predominated in the clinical picture of the girl. These rather unusual manifestations of sarcoidosis prompted an exploratory excision of tissue from the patient's spleen. Microscopic examination of the specimen showed reticular fibrosis with numerous small granulomas of epithelioid cells. This finding established the diagnosis of sarcoidosis, and treatment with desoxycorticosterone acetate (Decortin) was instituted. Three courses with total doses of 130 mg., 300 mg., and 220 mg. resulted in considerable improvement of the general condition, but there was no change in the blood picture. The patient was discharged from the hospital but was readmitted after 7 weeks. The size of the spleen had increased, and an additional course of Decortin therapy with a total dose of 245 mg. was ineffective. Splenectomy resulted in an improved general condition and a rapid remission of the abnormal blood findings.

Mild dyspnea, generalized swelling of lymph nodes, pronounced widening of the hili, and dense involvement of the lower lung field by miliary foci characterized the clinical picture of the boy. Microscopic examination of an excised cervical lymph node revealed productively built epithelioid-cell tubercles without giant cells and without caseation. Tuberculostatic therapy was ineffective, but treatment with 3 Gm. of cortisone as a total dose within 4 weeks resulted in a reduction of the size of the lymph nodes, less widening of the hili, and reduction of the miliary foci. New foci developed in the lungs, and the size of the lymph nodes increased again after discontinuation of cortisone therapy; the patient died of tuberculous meningitis. Although cortisone therapy exerted a beneficial effect on the granulomatous foci, it favored the development of active tuberculosis.

The cases of 148 children with sarcoidosis were collected from the literature. There were 78 boys and 63 girls, and in 7 the sex was not mentioned; 26 of these children were aged less than 8 years,

and the remaining 122 were between the ages of 8 and 15 years, thus showing a marked increase in the incidence of sarcoidosis in children older than 8 years of age. Pulmonary changes, hypercalcemia with calcium deposits in the spleen and kidneys, increased size of the spleen, and generalized lymph node swelling were also reported in some of these patients. The various clinical and histological observations in children with sarcoidosis favor the concept that bilateral swelling of the lymph nodes of the hilus represents the initial stage of sarcoidosis. Although local tuberculin sensitivity was reduced or missing in a large number of these children, this finding should not be interpreted as freedom from tuberculosis. Cortisone seems to be the only drug which may exert a favorable effect in some patients with sarcoidosis, particularly during the first and second stages of the disease. The risk of the occurrence of active tuberculosis, however, must be kept in mind, and, therefore, the administration of small doses of the drug seems to be advisable. In the presence of hypercalcemia, nephrocalcinosis, and involvement of the hematopoietic system, the indications and contraindications to cortisone therapy should be carefully weighed, if one does not want to omit it entirely.

Arterial Hypertension Attributed to Unilateral Renal Malformation. V. Saputo, F. B. Nicolis and C. Cattaneo. Acta paediat. latina 12:21-33 (Jan.-Feb.) 1959 (In Italian) [Reggio Emilia, Italy].

The authors discuss the case of an 11-year-old girl whose arterial blood pressure oscillated around 170 mm. Hg and occasionally reached peak values of 225 mm. Hg during the 6 years before admission. Occasional mild headache had been the only symptom accompanying hypertension. A considerable degree of diffuse edema of the retina without hemorrhage was observed on ophthalmological examination. Roentgenologic examination of the kidneys revealed a small atrophic left kidney and apparent absence of the corresponding adrenal gland, where the right kidney and the respective adrenal gland were larger than normal. The total renal function was normal. At operation, the left kidney, which was situated in an abnormally high position (between the 8th and 9th ribs), was entirely removed. Alternate areas of whitish and dark-red spots, along with several small cysts, covered the rough surface of this kidney. The renal artery and vein were of small caliber. The histological findings on the resected kidney revealed the presence of a diffuse arteriosclerosis associated with areas of infarction.

The patient's postoperative course was normal. The systemic arterial blood pressure decreased to 140/90 mm. Hg 13 days after the operation, and there was also a lower arterial pressure in the retina. Further improvement in the arterial blood pressure was observed on various examinations within the 18-month follow-up period. Nephrectomy produced in this child complete retrogression of the arterial hypertension despite its long duration before the operation. The authors suggest subjecting patients with arterial hypertension attributable to unilateral renal hypoplasia to nephrectomy; the operation is performed even in instances in which the hypertension is of long duration, provided that the total renal function is normal.

Contribution to the Knowledge of Transitory Corticoadrenal Insufficiency in the Newborn Infant. A. Disertori and M. Pasquale. Acta paediat. latina 12:34-44 (Jan.-Feb.) 1959 (In Italian) [Reggio Emilia, Italy].

The authors report on 2 newborn infants who, after 3 weeks of life, had episodes of disturbed digestion associated with dehydration and circulatory collapse. Profuse sweating in one infant and frequent episodes of circulatory collapse in the other led to hematochemical and hormonal investigations, which revealed a state of adrenal insufficiency in both patients. Decrease in the levels of serum sodium and chlorides (as chlorine), as well as of blood sugar, and increase in the serum potassium level were observed. There was also an increase in the eosinophil and lymphocyte counts. Both patients had normochromic anemia and a lower than normal body weight. Treatment with desoxycorticosterone acetate in daily doses of 2 mg., combined with adrenal cortex extract or cortisone, was instituted in each patient and produced a rapid improvement in general health and in symptoms, along with gain in body weight. The treatment was supplemented by either liver extracts or sodium chloride and glucose in the diet. Subsequent administration of corticotropin (ACTH) in small weekly doses restored the blood picture to normal.

The authors conclude that transitory corticoadrenal insufficiency affects to varying degrees all 3 zones of the adrenal cortex. This syndrome is probably related to the period of transformation of the adrenal cortex from the fetal into the fully developed phase. It starts when the infant is 2 or 3 weeks old but does not last more than 2 years. The therapy should be maintained until complete normalization of the clinical picture is obtained; otherwise, the symptoms may recur.

Coagulation Studies in the Newborn Period: III. Hemorrhagic Disease of the Newborn. A. J. Aballí, V. López Banús, S. de Lamerens and S. Rozengvaig. A. M. A. J. Dis. Child. 97:524-548 (May) 1959 [Chicago].

The authors report on 26 newborn infants, 16 boys and 10 girls, with hemorrhagic disease of the newborn, 17 of whom were studied by means of modern coagulation techniques before the institu-

tion of therapy at the General Calixto Garcia Hospital in Havana, Cuba, between 1955 and 1958. The findings in these patients were similar but much severer than those of so-called physiological hypoprothrombinemia of the newborn. The most outstanding changes were an almost complete depletion of proconvertin (stable blood factor), with a reduction of true prothrombin, and a very prolonged one-stage prothrombin time. The clotting time was prolonged, but the bleeding time was within normal limits. In addition, there was a marked alteration of the first stage of coagulation. The last-mentioned disturbance consisted of a pronounced decrease in thromboplastic activity of the serum due to a deficiency of several factors. These include plasma thromboplastic component (PTC) and a yet unidentified thromboplastic substance; it is possible that the latter may be the Stuart-Prower factor.

The same disorders can be demonstrated in infants with severe hypoprothrombinemia who do not show hemorrhagic manifestations. There is suggestive evidence that true PTC deficiency, and not loss of thromboplastic activity of serum, is related to the prolonged coagulation time and the tendency to bleed. The clotting defect in the newborn infant is similar to that produced by the prolonged use of coumarin derivatives. The changes observed in newborn infants with hemorrhagic disease respond spectacularly to the administration of vitamin K. If blood loss is severe, massive transfusions are imperative. Diagnosis of hemorrhagic disease rests on the demonstration of the characteristic coagulation defect in a very marked degree. Cases of anoxia complicated by multiple hemorrhages may constitute a separate entity. Alterations of blood clotting identical with those of hemorrhagic disease are present, but because of the pronounced fatty infiltration of the liver they do not respond to the administration of vitamin K. Capillary damage is also an important part of the picture, which greatly aggravates the hemorrhagic tendency. It leads to a positive reaction to the test of increased fragility and to a marked prolongation of the bleeding time. This variety is often fatal. The high incidence of hemorrhagic disease when no vitamin K prophylaxis is employed (and when no early artificial or complementary feeding is used) corroborates the advantages of the routine use of this vitamin in the newborn infant.

Coagulation Studies in the Newborn Period: IV. Deficiency of Stuart-Prower Factor as a Part of the Clotting Defect of the Newborn. A. J. Aballi, V. López Banús, S. de Lamerens and S. Rozengvaig. A. M. A. J. Dis. Child. 97:549-554 (May) 1959 [Chicago].

In an attempt at direct demonstration of the Stuart-Prower factor in newborn infants, serums were obtained from normal infants who did not show hemorrhagic manifestations. Various mixtures of these serums with that of a patient with Stuart-Prower deficiency, with hemophilia B serum kept in deep freeze, and with stored adult serum were subjected to the thromboplastin generation test and the test for determination of proconvertin. Additional experiments were performed with mixtures of serums obtained from untreated infants and from infants who had received vitamin K therapy. The results provided abundant evidence indicating the existence of a deficiency of the Stuart-Prower factor in the serums of newborn infants. This was particularly marked in those infants who had not received vitamin K. A presumptive test for the determination of the Stuart-Prower factor with use of a mixture of Loeliger-Kollar reagent for proconvertin and Stuart-Prower-deficient serum was tried, and it gave abnormal results in every case, again revealing the greatest change in untreated newborn infants. These findings show that a deficiency of the Stuart-Prower factor is an important part of the clotting defect of the full-term newborn infant.

DERMATOLOGY

Urticaria Pigmentosa (Mastocytosis): A Study of Nine Cases with Special Reference to the Excretion of Histamine in Urine. N. Brogren, H. Duner, B. Hamrin and others. Acta med. scandinav. 163: 223-233 (no. 3) 1959 (In English) [Stockholm].

The authors report on 5 male and 4 female patients, between the ages of 6 months and 63 years, with urticaria pigmentosa. Skeletal changes were observed roentgenographically in 5 of the 9 patients. These changes had the appearance of a diffuse and widespread osteosclerotic-osteoporotic process of pagetoid appearance, being most conspicuous in the pelvis (to which it was limited in 2 patients), vertebral bodies, and ribs but observed also in the clavicles, calvaria, and long bones of the extremities. An undoubtedly abnormal skeletal structure of this type was present in 3 of the 5 patients, while owing to the diffuse character of the roentgen-ray findings they were classed as questionably abnormal in the other 2.

The excretion of histamine and of 5-hydroxyindoleacetic acid (5-HIAA) in the urine was determined in all the patients. Abnormal histaminuria was found to be more or less pronounced in all 9 patients, but there was no increase in 5-HIAA. The remarkable increase in urinary histamine excretion seems to prove that the mastocytes, which constitute the histopathological basis of the urticaria pigmentosa, are producing excessive amounts of this substance. In one patient, the extirpation of a single cutaneous infiltrate was followed by a drop in the histaminuria to normal value. One patient showed severe intolerance to acetylsalicylic acid; a severe anaphylactic reaction with shock, erythema,

gastric hypersecretion, and increased histaminuria occurred in this patient after a small test dose. It is tempting to assume that in this patient the acetylsalicylic acid acted as a histamine liberator and that the amount of histamine stored in the patient's body was unusually large because of her "mastocytosis." Mastocytosis (the term suggested for urticaria pigmentosa because of the role played by mast cells in this disease) is obviously a clinical parallel to carcinoidosis with signs of overproduction of histamine in the former disease and of 5-hydroxytryptamine in the latter.

Mutilating Porphyria: Case. P. A. Viglioglia, J. Viglioglia, R. O. Linares and J. Vidiella. Prensa méd. argent. 45:3671-3677 (Nov. 21) 1958 (In Spanish) [Buenos Aires].

Mutilating porphyria is a rare familial disease due to imbalance of the metabolism of porphyrins. It involves mainly certain regions of the skin and of the mucosa and certain viscera. It appears in children or adolescents and rarely in adults. It starts with the features of cutaneous porphyria and progresses with the development of photosensitiveness of the skin, increased susceptibility of the skin and the nails to even minimal trauma, increased allergy-like reaction to certain substances, marked pigmentation of the skin, cutaneous lesions, retention of porphyrins in the tissues, and elimination of porphyrins in the urine. The cutaneous lesions consist of recurrent vesicles of serohemorrhagic fluid or of pus, which break up, turn into ulcers, form deeply seated scars, and cause atrophy and retraction of the skin and of the mucosa. The tissues become necrotic and slough off, causing mutilation of the lips, nose, eyelids, ears, and hands. The atrophic pigmented facial skin becomes firmly attached to the facial bones. Facial movements are lost. The face acquires a cadaveric look. Lesions of the eyes cause blindness. The fingers are shortened and ankylosed.

Two patients with typical mutilating porphyria were observed by the authors in the departments of hematology and dermatology of the Rawson Hospital, of Buenos Aires, between 1956 and 1958. The patients were men, 25 and 55 years of age respectively. The skin disease and photosensitiveness of the skin appeared in childhood in both patients. The younger patient was blind from ocular lesions of porphyria. The older patient had chronic conjunctivitis and ocular lesions with preservation of a fair vision. He had a brother with the same disease. Erythropoiesis, the bone marrow material taken by sternal puncture, and the peripheral blood were normal in both patients. The hepatogram showed impaired function of the liver; the results of puncture biopsy of the liver showed cirrhosis. A biopsy of the hands showed the histological features of mutilating porphyria. Both patients had diffuse hypertrichosis, a cadaveric face, mutilation from atrophy and decay of the skin at the lips, nose, eyelids, and ears, and shortening of the fingers, as verified by roentgen-ray examination.

The authors conclude that mutilating porphyria of either the erythropoietic or the hepatic form is severe and of long duration. The visceral involvement is more severe than the external mutilation caused by the disease. According to whether the disease is hepatic or erythropoietic, death is due to cirrhosis of the liver or to severe changes in the blood; in rare cases it is due to intercurrent disease.

OPHTHALMOLOGY

Internuclear Ophthalmoplegia: A Review of 58 Cases. J. L. Smith and D. G. Cogan. A. M. A. Arch. Ophth. 61:687-694 (May) 1959 [Chicago].

The syndrome of internuclear ophthalmoplegia is a characteristic disturbance of ocular motility. This study is based on 58 cases of internuclear ophthalmoplegia, 29 of which were unilateral and 29 bilateral. The unilateral and bilateral forms of internuclear ophthalmoplegia are relatively distinct entities. Unilateral internuclear ophthalmoplegia occurs more frequently in men and at any age but most often in the older age group. It typically involves the right side and lasts only a few weeks but may last for years. It is apt to occur in patients with hypertension or diabetes and appears to be due to a vascular lesion in the pons. While the medial rectus is paralyzed on conjugate gaze, its function is usually preserved for convergence. Vertical nystagmus is frequent but not constant. Skew deviation is frequent. The commoner neurological signs associated with unilateral internuclear ophthalmoplegia are transient cerebellar signs and dizziness at onset. Trigeminal paresthesias are often present around the mouth and lips on either side. The 5th and 7th cranial nerves are the most frequently involved in these patients, and conjugate gaze paresis occurs occasionally. The internuclear palsy may clear completely, but 4 patients in this series died within 2 months of developing this lesion. The prognosis must be guarded.

Bilateral internuclear ophthalmoplegia occurs in men and women equally, and at any age. Bilateral involvement is almost invariably indicative of multiple sclerosis. This was the diagnosis in 28 of the 29 patients with the bilateral form in this series. Vertical nystagmus is usually present on upward gaze. Skew deviation is infrequent in the bilateral cases. The commoner neurological signs associated with bilateral internuclear ophthalmoplegia are trigeminal neuralgia, long-motor tract signs, frequently bilateral Babinski responses, cerebellar signs, scanning speech, and absent abdominal reflexes. Not all these signs are present at onset of

the internuclear palsy but develop at some time during the course of the illness, as is expected in multiple sclerosis. The prognosis in these cases is as unpredictable as it is in multiple sclerosis in general. As the syndrome may clear and no further evidences of multiple sclerosis may ensue for years, this may be pointed out to the patient. On the other hand, of 6 patients with bilateral internuclear palsies who died, death occurred at an average of 83 months after the internuclear palsy had first been noted (range, 18 to 144 months).

Iridencleisis: Technique and Results in Ninety-Five Consecutive Operations. M. W. Haisten and J. S. Guyton. A. M. A. Arch. Ophth. 61:727-737 (May) 1959 [Chicago].

It is generally accepted that iridencleisis lowers the intraocular tension, at least in part, by creating a fistula through which aqueous can drain to the subconjunctival bed. The fluid is then absorbed or, in the case of a thin cystic bleb, may pass transconjunctivally to mix with the tears. This mode of action of iridencleisis appears substantiated clinically by the fact that a good conjunctival bleb is usually associated with control of the intraocular tension, and, conversely, absence of the bleb is usually associated with lack of control. The technique of iridencleisis is described, and certain phases of it are discussed, such as the dissection of the conjunctival flap, the scleral incision, the relative merits of one-pillar or two-pillar iridencleisis, iris manipulation, and iridodialysis.

From Jan. 1, 1954, to June 30, 1957, the authors performed iridencleisis at the Henry Ford Hospital in Detroit for various types of glaucoma on 95 eyes of 71 patients (31 men and 40 women). The operation was performed on both eyes in 24 patients. The operation is regarded as successful only if the following requirements are met: 1. The tension must be controlled. 2. There must be no progressive loss of visual field after surgery. 3. There must be no permanent and disabling injury to the eye as a result of the surgical procedure. Classified according to these criteria, a successful result was obtained in 72 of the 86 cases followed for a minimum of 4 months. Miotics were required in 18 of the 72 cases classified as having a successful result. The operation failed in 14 eyes.

For the purpose of analyzing results obtained, the 86 cases with adequate follow-up have been classified into 1 of 3 categories: acute congestive glaucoma, chronic open-angle glaucoma, and chronic narrow-angle glaucoma. Iridencleisis was not utilized in the treatment of aphakic glaucoma, secondary glaucoma, or congenital glaucoma. The authors believe that iridencleisis is the operation of choice in those cases of acute congestive glaucoma in which permanent embarrassment of the outflow mechanism has occurred. Iridencleisis and cyclodialysis are of comparable effectiveness for chronic primary noncongestive glaucoma of either the open-angle or the narrow-angle type (with the exception of cases occurring in the Negro race, in which the authors prefer cyclodialysis). They do not feel that iridencleisis is indicated in aphakic or other secondary glaucomas.

THERAPEUTICS

Treatment of Cardiac Shock by Metaraminol. E. M. M. Besterman. Brit. M. J. 1:1081-1083 (April 25) 1959 [London].

Metaraminol bitartrate seems to possess the properties of direct action on the heart as well as on the peripheral resistance. It may be administered by repeated injections without the development of tachyphylaxis. Metaraminol produces a sustained increase of myocardial contractility without requiring increased coronary flow per unit of ventricular work. This central action, together with the peripheral effects, achieves the most desirable results, namely, increased arterial pressure and cardiac output at a low atrial pressure. Metaraminol has a similar action to that of arterenol but has the advantage that it may be given by subcutaneous, intramuscular, or intravenous injection. The author reports on 12 patients with cardiac shock who received treatment with metaraminol by intermittent injection. Six of the 12 patients died, the deaths of 5 occurring within 6 hours of the onset of shock. In all the patients who survived, shock developed after admission to hospital. They were, therefore, treated within 15 to 30 minutes of the onset. With one exception, pressor therapy had to be maintained for a minimum of 12 hours. Three patients required metaraminol for 24 to 36 hours, and one patient for nearly 6 days. The average hourly dose of the drug was 1.3 mg. in 3 cases and 0.9 to 1.3 mg. in the remaining 3 cases.

The initial intravenous dose of metaraminol should not exceed 1.25 mg. A dose of 2.5 mg. may be given by the intramuscular or the subcutaneous route, subsequent doses being determined by the pressor response. The pressor effects of intravenously administered metaraminol appear within 3 minutes and persist for 10 to 30 minutes. The response to intramuscular injection occurs within 10 to 20 minutes and lasts 1 to 3 hours, whereas the pressor action appears 30 to 45 minutes after subcutaneous injection and persists for 2 to 4 hours. In severe shock, absorption from subcutaneous injections is poor, and intramuscular injections may be used after the initial one. The author points out that the use of increasingly larger doses of mephentermine would have achieved a pressor response in these patients of this series, but the repeated efficiency of identical doses of metaraminol has proved to be of great value. Metaraminol bitartrate is, therefore,

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the drug of choice for intermittent parenteral use in cardiac shock and should be of particular benefit in the domiciliary treatment of this condition.

Evaluation of Anticoagulant Therapy With Anisindione (Miradon). W. F. Connell and G. A. Mayer. Canad. M. A. J. 80:785-790 (May 15) 1959 [Toronto].

Preliminary reports on the new anticoagulant preparation, anisindione (Miradon), were sufficiently favorable to induce the authors to undertake a clinical evaluation in 169 patients at the Kingston (Ont.) General Hospital during the period from October, 1957, to September, 1958. Of these patients, 58 had acute myocardial infarction, 62 acute coronary insufficiency, 18 acute thrombophlebitis, 16 pulmonary embolism, and 4 cerebral thrombosis; the remaining 11 received the therapy for miscellaneous reasons, including postoperative prophylaxis. The age-range was from 27 to 81 years. There were 113 men and 56 women. Ninety-eight patients included in this short-term study are still taking Miradon on a long-term basis. The standard clotting time (SCT) of unmodified whole blood was measured by the method of Mayer. Normal values for this technique are 11.9±0.9 minutes. In most patients treatment was begun by the intravenous injection of 100 mg. of heparin and by the simultaneous oral administration of 500 mg. of Miradon. Of the 169 patients, 27 did not receive heparin, since an immediate anticoagulant effect was not required. A supplement of 500 mg. of ascorbic acid daily was routinely prescribed. Heparin therapy was maintained by further 100-mg. intravenous injections at intervals of 6 or 7 hours during the day and 8 to 10 hours at night. Control tests were carried out before the first morning dose of heparin, and hence 8 to 10 hours after the bedtime dose. When the SCT had risen to 15 minutes, heparin was given only at 12-hour intervals; when a level of 16 to 17 minutes was achieved, heparin was withdrawn. All the patients received 500 mg. of Miradon on admission, 300 mg. on the second and third days, and 200 mg. on the fourth day. This routine was very satisfactory in most cases.

A satisfactory therapeutic prolongation of the standard clotting time was achieved within 3 days in patients receiving heparin initially; without heparin a therapeutic prolongation of the SCT was achieved within 4 days. Ninety-one per cent of all the SCT readings were within the therapeutic range; thus, control of Miradon therapy is comparatively easy with this technique. For the maintenance of a steady therapeutic effect, it is necessary to administer Miradon on a daily dosage schedule. The daily maintenance schedule must be individualized according to the SCT, and the requirement may range from 25 to 175 mg. Vitamin K_1 (Konakion) in 20-mg. doses, either orally or intravenously, will lower an unduly prolonged SCT to safe levels within 5 to 8 hours. While one thromboembolic complication and 10 hemorrhagic episodes are reported in this series, none of these complications occurred while the SCT was within the therapeutic range. As in previous studies, the authors were unable to demonstrate a significant statistical correlation between the standard clotting time and the Quick one-stage prothrombin test. Miradon is an excellent anticoagulant for oral administration. The authors now use it extensively for both short-term and long-term anticoagulant therapy.

Clinical Experience with DBI (Phenformin) in the Management of Diabetes. J. B. R. McKendry, K. Kuwayti and P. P. Rado. Canad. M. A. J. 80:773-778 (May 15) 1959 [Toronto].

Phenformin (DBI) or phenylethyldiguanide is structurally related to the diguanidine, Synthalin, one of the first orally effective hypoglycemic agents which was discovered and tested about 30 years ago but which unfortunately proved toxic, especially to the liver. Reviewing earlier investigations on phenylethyldiguanide, the authors point out that its mode of action is not entirely understood. The fact that it lowers the blood sugar level in diabetics is apparently not associated with inhibition of adrenal cortical activity, since excretion of 17-hydroxycorticosteroids and 17-ketosteroids and nitrogen remains unaltered. There is likewise no inhibition of glucagon activity. There are increases in blood pyruvate and lactate consistent with the conclusions from in vitro studies that the drug encourages anaerobic glycolysis. This action seems to be unaccompanied by deleterious effects, since no toxic manifestations have been reported in clinical studies involving hundreds of patients and extending over periods of more than 2 years.

The authors began clinical trials with the oral administration of phenylethyldiguanide (Phenformin) at the beginning of 1958. The diabetic patients were from the metabolism service of the Ottawa Civic Hospital and the private practice and outpatient clinic of one of the authors. In a series of 58 diabetic patients, the oral administration of Phenformin resulted in a satisfactory response in 35 and either failed to produce sufficient hypoglycemic effect or caused intolerable side-effects in the remaining 23 patients, classified as failures. All the successes were not complete successes, though, and others might become intolerant of the drug as they used it longer. On the other hand, it is felt that some of the failures might have become successes if the opportunity had been afforded for more prolonged and painstaking adjustment of dosage, particularly with the benefit of experience obtained later.

The authors feel that their experience indicates that Phenformin merits a place in the management of diabetes, particularly in that group of patients in whom previous methods have been least ade-

quate, i. e., the unstable case of both juvenile and adult types. The drug is capable of restoring control in a considerable portion of patients in whom sulfonylurea compounds have failed. One difficulty in the employment of Phenformin is the prevalence of gastrointestinal side-effects, which, however, are partly avoidable by careful attention to dosage schedule. Toxic effects have not been encountered, and it does not appear that secondary development of refractoriness will be common.

Antibiotics in the Therapy of Leptospiral Infections. O. Gsell. Schweiz. med. Wchnschr. 89:422-425 (April 18) 1959 (In German) [Basel, Switzerland].

Bacteriostatic as well as bactericidal effects of penicillin, streptomycin, and the broad-spectrum antibiotics on Leptospira organisms have been demonstrated experimentally by in vitro and in vivo tests. Opinions vary widely, however, with regard to the clinical value of antibiotic therapy in leptospiral infections. The author reviews observations on 222 patients with leptospiral disease, of whom 122 were treated with antibiotics; the other 100 patients served as controls. These patients were observed at several canton hospitals in Switzerland. Illness in swineherds and so-called field fever were the most common clinical forms. Penicillin was used in 51 of the patients, streptomycin in 2, and broad-spectrum antibiotics (Aureomycin, Terramycin, tetracycline, erythromycin, and others) in 69 patients. Treatment was usually begun shortly after admission, after the history, temperature, blood picture, and spinal puncture had been completed, and the diagnosis of leptospirosis seemed probable on clinical and epidemiologic grounds. Culture of Leptospira organisms from blood and cerebrospinal fluid was not always successful. The clinical picture, serous meningitis of mild or moderate severity, was rather uniform and usually benign, regardless of the causal type of Leptospira (Lept. pomona, Lept. grippotyphosa, Lept. icterohemorrhagiae, Lept. canicola, etc.). Only 8 of 9 infections with Lept. icterohemorrhagiae and 1 with Lept. canicola were somewhat more severe.

The following were regarded as criteria for the efficacy of antibiotic therapy in leptospirosis: prevention of the second phase of fever; prevention of elevation of the cell count in the cerebrospinal fluid during the second week; prevention of elevation of the specific agglutination titer to over 1:200 during the second or third week; and shortening of the total duration of fever. When treatment with broad-spectrum antibiotics was begun on the first or second day, it was almost 100% successful. When it was begun on the third or fourth day, it prevented the second phase of fever in 65% and an increase in agglutination titer in 39%, but it influenced the serous meningitis in only 4%. The total duration of fever was shortened whenever treatment was begun before the fifth day. When antibiotic therapy was begun after the fifth day, it proved ineffective.

Daily doses of 600,000 units of penicillin were less effective than was treatment with the broad-spectrum antibiotics. The author advises that the latter be given in daily doses of 1 to 2 Gm. by mouth. Penicillin should be given in daily doses of at least 2.4 million units. There were practically no differences in the efficacy of the broad-spectrum antibiotics, except that Chloromycetin was somewhat less effective than were some of the others. Early treatment (before the fourth day) in 3 patients with Lept. icterohemorrhagiae infection prevented jaundice, but the author believes that this effect would have to be verified on a larger group of patients. He recommends antibiotic therapy for all forms of leptospiroses.

First Orientations on the Therapeutic Possibilities of Dexamethasone in Rheumatology. T. Galli and C. Mannetti. Minerva med. 50:949-953 (March 31) 1959 (In Italian) [Turin, Italy].

Clinical effects of dexamethasone were studied in 52 patients with various rheumatic diseases. Rheumatoid arthritis was present in 24 patients, rheumatic fever in 6, acute arthrosis in 15, acute gout in 6, and chronic gouty polyarthritis in 1. Dexamethasone produced the following effects among the 24 patients with rheumatoid arthritis: Initial daily dosage of 4 or 3 mg. and maintenance dosages from 1.5 to 1 mg. proved to be the optimum doses for the relief of symptoms in 5 patients who had not previously received any steroid treatment. Dexamethasone could be substituted for prednisone in dosages of a ratio of 1/10 in most of the 10 patients who attained stabilization of the disease with maintenance doses of prednisone. Dosages of Dexamethasone in a ratio of 1/10 as compared with prednisone brought relief of symptoms in 4 of the 5 patients in whom the maintenance dosage of prednisone had become inefficacious. Treatment with high maintenance doses of prednisone, which had been administered to 2 patients for a year, caused a tendency toward retention of fluids; substitution of dexamethasone for prednisone produced only a transitory disappearance of the edema. Treatment with high maintenance doses of prednisone in 2 other patients caused the appearance of glycosuria; substitution of dexamethasone for prednisone in doses of from 1 to 1.75 mg. had the same therapeutic effect as prednisone but without accompanying glycosuria.

In the treatment of the 6 patients with rheumatic fever, the initial daily dosage of 3 mg. of dexamethasone produced improvement within 10 days in 3 patients who had not previously received prednisone; the 3 patients who had previously been treated with prednisone derived further benefit

after being given dexamethasone. Although dexamethasone had a rapid and marked therapeutic action in patients with rheumatic fever, it is as yet too early to appraise its therapeutic value as compared with prednisone. The antalgic and anti-inflammatory action of dexamethasone, as compared with other steroids, seemed to be more rapid and more complete in the 15 patients with acute arthrosis. The administration of a dosage of dexamethasone in a ratio of 1/7 as compared with prednisone gave equal or superior results, without the accompaniment of undesirable side-effects, in the 6 patients with acute gout who had previously been successfully treated with prednisone for periodic episodes of the disease during the past years. The administration of a daily dose of 1 mg. of dexamethasone effectively replaced the administration of 15-mg. (or higher) daily doses of prednisone in a 19-year-old patient who had had chronic gouty polyarthritis for the past 9 years. The few mild side-effects observed with dexamethasone therapy were sweating, redness of the skin, pain in the stomach, diarrhea, and moon face. Dexamethasone may not be useful for treatment over a long period of time, because it has a high inhibitory effect on the adrenal glands. This investigation suggests its use mostly for short periods in treating those acute diseases which are not of long duration.

Metabolic Effects and Clinical Results of Dexamethasone in the Treatment of Bronchial Asthma. V. Cagli, U. De Nardo and G. Raymondi. Minerva med. 50:941-945 (March 31) 1959 (In Italian) [Turin, Italy].

Dexamethasone was administered to 8 patients, aged between 13 and 43 years, who had had bronchial asthma for a long time, and some of whom had previously been treated with other cortisone derivatives. The initial daily dosage of 3 to 5 mg. of dexamethasone was administered in 4 equally divided doses. The daily dosage was reduced to 3 or 2 mg. after several days of treatment. All the patients received a daily maintenance dose, varying from 2 to 0.5 mg. for the remaining period, which ran up to 60 days. Complete remission of the symptoms was obtained in 5 patients whose symptoms had been severe. The intensity of the symptoms diminished considerably in one patient and subsided completely in another with a mild variety of the disease. One patient derived no benefit from the treatment. In general, improvement of the symptoms was observed within 3 to 6 days, and partial or total remission was obtained after 8 to 12 days of treatment. The patients tolerated the drug well and gained in weight.

The metabolic effect of dexamethasone was studied in 6 patients. The level of urinary 17-ketosteroids decreased, that of 11-oxysteroids tended to decrease, and that of 17-hydroxycorticosterone remained unchanged. A dose of 2 mg. of the drug caused a considerable decrease in the count of circulating eosinophils, which in 4 patients fell 65 to 85% as compared with the number per cubic millimeter recorded before treatment. No significant changes were observed in the blood sugar level, in the serum electrolyte value, and in the level of acidity of the stomach. The main comparative clinical advantage of dexamethasone over other steroids seems to lie, not in a greater therapeutic efficacy, but rather in the possibility of using smaller doses.

The Oleandomycin-Tetracycline Combination Used Locally and Generally in the Treatment of Pleural or Extrapleural Empyema in Patients with Pulmonary Tuberculosis: Preliminary Note. V. Gramazio, B. Occhialini and E. Volpe. Ann. med. Sondalo 7:33-35 (Jan.-Feb.) 1959 (In Italian) [Sondrio, Italy].

The authors report on 30 patients with pulmonary tuberculosis, with pleural or extrapleural empyema, who since June, 1957, have been treated with Sigmamycin, an oleandomycin-tetracycline combination. The empyema cavity had been drained according to Bülau's treatment in 18 patients, but it had not been drained in the remaining 12 patients; the condition of empyema had been present for from 6 months to 8 years. Half of the patients had a bronchopleural fistula, and most of them were in poor general condition and had fever. Pus to the extent of 50 to 90 cc. was found daily in the expectorations of 2 patients with bronchopleural fistulas which had not been drained; in the other patients, 50 to 150 cc. of pus was eliminated from the cavities daily. All the patients had derived little or no benefit from previous treatment with sulfonamides or with other antibiotics. The isolated bacterial flora was often mixed. Staphylococcus pyogenes var. aureus was observed very frequently; Pseudomonas aeruginosa was observed less frequently; and Diplococcus pneumoniae and Proteus organisms were observed in a few patients only.

Sigmamycin was administered by mouth in a few patients only at the rate of 1 Gm. per day for at least 10 days. In most patients the drug was instilled into the empyema cavity, 250 mg. being diluted in 10 cc. of distilled water or physiological serum, after removal of the exudate and lavage. Two patients received Sigmamycin intravenously, 250 mg. per day in 250 cc. of physiological serum; the drug was also instilled locally in these 2 patients. The drainage tube was kept closed for 3 or 4 hours after instillation of the antibiotic into the empyema cavity in patients subjected to Bülau's treatment. Temporary fever followed the drug's instillation in a few patients. Toxic symptoms disappeared rapidly in all the patients; the exudate diminished and became fluid or clear; and pyogenic

germs disappeared from the exudate in two-thirds of the patients. Sigmamycin was most effective when administered locally or when given by mouth or intravenously.

Topical Steroids in Diseases of the Colon. M. Patterson and J. McGivney. South. M. J. 52:423-428 (April) 1959 [Birmingham, Ala.].

The authors report on 47 patients with diseases of the colon who received topical steroid therapy at the University of Texas Medical Branch Hospitals in Galveston. Of the 47 patients, 20 with factitial (radiation) proctitis were treated with 10-mg. hydrocortisone acetate suppositories (Wyanoid HC) or 25 mg. of hydrocortisone acetate suspended in 60 or 90 cc. of water and instilled into the rectum 2 or 3 times a day. Prompt symptomatic relief was observed in 17 of these 20 patients, and 3 were therapeutic failures. The 17 patients were followed up for 6 months, and, aside from less hyperemia and bleeding, proctoscopic healing was observed in only 4. Twenty-seven patients with idiopathic ulcerative colitis were treated by means of 3 methods of therapy: 1. Suppositories containing 10 or 15 mg. of hydrocortisone acetate were used for patients with mild disease limited to the rectum or rectosigmoid. 2. For those with further involvement of the colon, watery suspensions of 50 mg. of hydrocortisone acetate or 10 mg. of prednisone were used in rectal instillations 2 or 3 times a day. 3. For patients with more extensive involvement, a daily proctoclysis with 50 or 100 mg. of water-soluble hydrocortisone sodium succinate in 250 or 500 cc. of sodium chloride solution was given. Treatment was usually carried out for a 2-week period, but if early improvement was noted on proctoscopic examination and tissue changes were marked, the treatment was prolonged for several weeks. If a response was not apparent in 2 weeks, further therapy was considered useless and perhaps harmful. Rapid symptomatic improvement and remissions, as revealed by the proctoscope, were observed in 22 (81%) and 20 (77%) patients, respectively. The best results were obtained in early disease involving the rectum and rectosigmoid. One patient in whom a severe and bloody diarrhea developed after oral administration of antibiotics responded dramatically to rectal instillations of hydrocortisone.

The advantages of topical steroid therapy are the rapidity of response; improvement not only symptomatic but on proctoscopic examination; minimal detectable degrees of absorption, with avoidance of undesirable side-effects of prolonged steroid therapy; and maximum concentration of the medication in the area of involvement. The disadvantages are related to the unpredictable response; the difficulties in retention, which in most cases are related to anatomic difficulties rather than tenesmus; and, in one patient, the worsening of the proctoscopic and clinical picture in the course of treatment. The use of steroids in the form of a rectal instillation may offer a valuable adjunct in the treatment of acute exacerbations of ulcerative colitis. Frequent proctoscopic examinations are imperative.

Electrophysiological Analysis of Effects of Various Neuroleptic Drugs (Chlorpromazine, Reserpine, Tofranil, Meprobamate). M. Monnier and P. Krupp. Schweiz. med. Wchnschr. 89:430-433 (April 18) 1959 (In German) [Basel, Switzerland].

The various tranquilizing drugs differ in their effect on the diverse parts of the nervous system. The authors investigated the action of chlorpromazine, reserpine, Tofranil (brand of imipramine), and meprobamate by electrophysiological methods in rabbits. With the aid of a repeatedly described stereotaxic method, the electrical activity of different areas of the brain was recorded in 117 rabbits. It was found that chlorpromazine, reserpine, and imipramine influence the sympathetic nervous system, whereas this is not the case with meprobamate and a drug related to it and designated as Hg 532. In regard to the tranquilizing and sedative actions on somatic functions the drugs differ, and this becomes manifest in the electroencephalogram in the form of a pattern of "relaxation or sleep" with a reduced arousal reaction to external stimuli. The arousal system of the brain stem is generally depressed, especially by chlorpromazine and imipramine, whereas the mediothalamic system which depresses and synchronizes the cortical system is somewhat hyperactive, at least temporarily.

Reserpine is an exception because it stimulates rather than depresses the reticular system in the midbrain, and it depresses the thalamocortical projections of this system. This explains the tranquilizing effect of reserpine without an important hypnotic component, as well as the alert state with indifference to external stimuli. The action on the limbic system, the rhinencephalon and paleocortex, varies somewhat with the different drugs: there is slight stimulation after chlorpromazine or reserpine, no effect after imipramine, and slight depression after meprobamate. In addition to their tranquilizing effect, drugs of the meprobamate group, particularly Hg 532, slightly relax the muscle tonus.

Fasting as an Introduction to the Treatment of Obesity. W. L. Bloom. Metabolism 8:214-220 (May) 1959 [New York].

The author reports on 5 women and 4 men, between the ages of 20 and 60 years, who were obese and were treated by fasting for prolonged periods in the Piedmont Hospital, Atlanta, Ga. Six of the 9 patients had previously attempted to reduce but had failed. The fasts lasted from 4 to 9 days. Water was allowed ad libitum and, in some instances, tea or coffee without additions other than synthetic

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sweetening if desired. The patients were allowed the freedom of the floor of the hospital, but no exercise was included in the program. Prolonged total fasting with free access to water was well tolerated by the 9 obese patients. They had no intense hunger during their fasts and few undesirable symptoms, such as occasional mild headaches, easily relieved by an analgesic, and epigastric distress, which was relieved with water. During the fast, many reported a marked sense of well-being, suggesting a mild euphoria. Weight loss averaged 2.6 lb. (1.1 kg.) per day of fasting in the men, and 2.7 lb. (1.2 kg.) per day in the women. This weight loss exceeded that which could be explained by caloric energy expenditure or urinary water loss. Studies of urinary 17-hydroxysteroid excretion at the onset and termination of the fast showed no evidence of increased adrenal activity.

The fast was broken by the oral administration of dextrose in doses varying from 25 to 100 Gm. On resumption of eating, a 600 to 800 caloric diet was found to produce satiety, whereas, before the fast, this type of diet was unsatisfactory to the patient. Follow-up studies indicate that all patients have maintained a large part of the weight loss achieved during the fast, and most of them have continued to lose weight by dieting. This regimen has made it possible to reeducate the patient about proper eating habits without using tranquilizers, metabolic stimulants, artificial fillers, or central nervous system stimulants.

PATHOLOGY

Renal Angiomyolipomas: Report of Four Cases. H. J. Klapproth, E. F. Poutasse and J. B. Hazard. A. M. A. Arch. Path. 67:400-411 (April) 1959 [Chicago].

Renal angiomyolipomas represent a special type of the histopathologically interesting forms of hamartomas. The authors present the histories of 4 patients (3 women and 1 man) with renal hamartomas of the angiomyolipomatous type. None of the patients exhibited signs of tuberous sclerosis. The first patient who had a massive involvement of both kidneys, concomitant with bilateral polycystic disease, posed several therapeutic problems. The second patient had an unusually large hamartoma at the lower pole of the right kidney. The third patient had episodes of hematuria over 17 years, without any other signs and symptoms. A small filling defect of the lower calyx was recognized roentgenographically as a slowly growing lesion, and resection of the lower pole of the right kidney was performed. The angiomyolipoma measured only 1 cm. in diameter. In the fourth patient, acute pain in the right flank, a palpable tumor of the right kidney, and a filling defect, demonstrated by intravenous urography, were the indications for nephrectomy. The original diagnosis was liposarcoma, but additional sections led to the correct diagnosis of hamartoma of the angiomyolipomatous type. Fifteen previously published cases of angiomyolipoma are reviewed.

Renal angiomyolipomas are hamartomas that rarely occur in patients without lesions of the tuberous sclerosis complex and then are unifocal within the kidney. Histopathologically, they do not differ from the usually multiple renal hamartomas in patients with tuberous sclerosis. In contrast to the small medullary fibromas, angiomyolipomas may reach considerable size and produce the clinical symptoms of renal tumors, namely, pain, fever, and hematuria. They may, on the other hand, cause no symptoms at all. Hematuria is indicative of an angiomyolipomatous hamartoma only in patients with both chronic recurrent episodes and roentgenologic evidence of a slowly growing lesion. Angiomyolipomas are hamartomas, i. e., they are due to an error in development. A so-called malignant angiomyolipoma, therefore, cannot be labeled a malignant hamartoma but must be classified as a malignant tumor of mixed mesenchymal origin (malignant mesenchymoma). No evidence has yet been found that malignant changes do occur in hamartomas of the angiomyolipomatous type. Surgical removal of the hamartoma by either excision or nephrectomy is the only form of treatment. Immediate surgery is indicated in patients with acute symptoms of hemorrhage into tumor, kidney, or perirenal fat.

The Pathology of 1957 (Asian) Influenza. D. D. Mark. Am. Rev. Tuberc. 79:440-448 (April) 1959 [New York].

The pathological findings in the lungs in 17 fatal cases of Asian influenza which occurred during the 1957 epidemic were studied at the Johns Hopkins and the Baltimore City hospitals. The evidence of infection with influenza virus, type A (Asian strain), was established in the lungs of 6 patients, and the virus was isolated by hemagglutination antibody tests in 4. Most samples of pulmonary tissue yielded Staphylococcus pyogenes var. aureus, although one culture was sterile when positive serologic evidence of influenzal infection was obtained. Pneumococci were twice isolated in proved cases of influenza when no true suppurative pneumonia existed. The lungs of all the patients showed a characteristic necrotizing tracheobronchitis with foci of squamous metaplasia in the mucosa, which is considered as a characteristic feature of influenza virus infection. The study revealed that this infection may be clinically occult in patients with cardiovascular impairment. The necessity is emphasized for a more organized approach to the problem of isolating the influenza virus from affected as well as unaffected tissues, in the presence or absence of known or suspected influenzal infection. The importance of Staph. aureus as a predominant superinfecting organism in fatal cases is indicated.

Significance of Deposits of Calcium in the Pathogenesis of Tuberculoma of the Lung. E. Vincze and J. Kenéz. Beitr. Klin. Tuberk. **120:** 108-118 (no. 2) 1959 (In German) [Berlin].

The authors studied pulmonary lobes or segments with tuberculomas which were obtained by surgical resection from 92 patients with pulmonary tuberculosis treated in 2 sanatoriums in Hungary. The specimens were divided into 6 groups: 1. There were 15 cases of simultaneous occurrence of tuberculoma and manifest hematogenous chronic tuberculosis; in 12 of the 15 cases both processes were intrapulmonary, and in 3 the tuberculosis was extrapulmonary and the tuberculoma was pulmonary. 2. Multiple tuberculomas and hematogenous deposits of calcium were present in 21 cases and the deposits of calcium were observed inside and outside the tuberculoma. 3. Deposits of calcium were observed in solitary tuberculomas in 43 cases. 4. In 5 cases of solitary tuberculoma there was no unequivocal pathogenic connection with the deposits of calcium. 5. Tuberculomas without calcium or traces of an old dissemination were found in 6 cases. 6. A tuberculoma originated from a primary focus in 2 cases. In groups 1 to 3 the pathogenetic significance of the deposits of calcium in the development of tuberculoma cannot be doubted; the clinical data of the patients from whom these specimens were obtained also favored this concept. In group 4, those cases were included in which remainders of the hematogenous dissemination were recognizable only outside the tuberculoma; the extensive caseous necrosis itself did not contain deposits of calcium. Tuberculomas of homogeneous structure or similar tuberculous manifestations were included in group 5. The differentiation of group 6 from group 3 is necessary, even if the exact differentiation is possible only in a small number of cases. From the roentgenologic and clinical points of view, the 92 cases were divided into 4 groups: 46 cases of tuberculoma in layers, 20 cases of tuberculosis with nodular conglomerations, 15 cases of filled-up cavities, and 11 miscellaneous cases.

The pathological examination of pulmonary tuberculomas showed that hematogenous deposits of calcium may be observed regularly not only inside the tuberculoma but also outside of it and at its periphery. One may observe most frequently several deposits of calcium, and an appositional structure can be recognized in the surrounding area. A tuberculoma may also develop in patients with hematogenous disseminated pulmonary tuberculosis, particularly in areas with confluent foci. From the pathogenic point of view, the tuberculoma is to be considered as a secondary manifestation; the characteristic structure is either nodular or conglomerated. In the development of tuberculoma the hematogenous deposits of calcium and also the caseous foci of nodular tuberculosis (the hematogenous origin of which is controversial) may be considered as primary manifestations. The authors' pathogenic concept seems to be confirmed by the occurrence of deposits of calcium in the tuberculomas and by the fact that a similar mechanism occurs also with other manifestations of pulmonary tuberculosis. The structure of the tuberculoma or its pathogenic factors were suggested by the results of the clinical examination in a small number of cases only. The clinical significance of the authors' study is seen in the fact that pulmonary tuberculomas cannot be considered as isolated lesions and that one should be on the lookout for other changes which may indicate hematogenous dissemination. The general rules for the treatment of hematogenous pulmonary tuberculosis should be applied with respect to therapy.

The Efficacy of Chloromycetin in the Treatment of Strangulation Obstruction. W. O. Barnett. Ann. Surg. **149:**471-474 (April) 1959 [Philadelphia].

The peritoneal cavities of animals dying of experimental strangulation obstruction of the lower small intestine have been shown to be the site of accumulation of large amounts of fluid. This prompted the author to report on experiments on 6 unselected adult mongrel dogs in order to determine the effects of a broad-spectrum antibiotic, Chloromycetin, on the toxicity of this fluid. Results showed that the peritoneal fluid which results from strangulation obstruction of the lower small intestine is toxic when injected into the peritoneal cavities of normal animals. Chloromycetin will eliminate the toxicity of the resulting peritoneal fluid when placed inside the lumen of the strangulated intestine. Nontoxic fluid results when Chloromycetin is placed in a plastic bag along with the strangulated intestine. The survival of normal animals is markedly improved by the intraperitoneal administration of Chloromycetin simultaneously with the toxic strangulation obstruction fluid. These findings support the role of bacteria in the lethal issue of strangulation obstruction.

Disseminated Intravascular Coagulation: A Cause of Shock. R. M. Hardaway and D. G. McKay. Ann. Surg. **149:**462-470 (April) 1959 [Philadelphia].

The authors report on experiments made on 36 mongrel dogs of both sexes to demonstrate that certain types of shock are due to intravascular clotting. The dogs were divided into 4 groups. Group 1 was given injections of incompatible blood alone; group 2 was given heparin plus incompatible blood; group 3 was given amniotic fluid alone; and group 4 received amniotic fluid plus heparin. Occasionally the injection of heparin caused a drop in blood pressure, but this rose quickly to normal levels before the start of the experiment. The investigations also showed that shock due to amniotic fluid embolization can be prevented by pretreatment with heparin; therefore, it is suggested that the major portion of the shock in this condition is due to intravascular coagulation. Shock resulting from injection

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of incompatible blood was partially, but not completely, prevented by heparinization. These observations point to the probability that intravascular coagulation may be entirely or partially responsible for reversible shock. Portal vein pressure was elevated in this type of shock, while systemic vein pressure fell. Pulmonary blood pressure was apparently elevated in this type of shock, since there was an apparent increase in pulmonary resistance. There is some evidence that shock may be due to a decreased cardiac output secondary to (*a*) acute cor pulmonale or (*b*) decreased venous return to the heart. The former may be due to intravascular thrombi in the lungs plus associated vascular spasm damming the flow of blood. The latter may be due to thrombosis and associated vascular spasm in the small vessels of the liver with consequent damming of blood in the portal system.

RADIOLOGY

Study of Six Cases of Accidental Acute Total Irradiation. H. Jammet, G. Mathé, B. Pendic and others. Rev. franç. étud. clin. et biol. 4:210-225 (March) 1959 (In French) [Paris].

Six persons working near an atomic reactor at the Center for Nuclear Studies at Vinca, Jugoslavia, accidentally received sublethal (1), lethal (4), and supralethal (1) doses of radiation. They were brought to Paris the following day and were admitted to the service of radiopathology at the Curie Foundation. Exact evaluation of the amount of radiation received by each was difficult, and the calculations were unavoidably lacking in precision; consequently, in determining the therapeutic indications, which depend on the amount of radiation received, it was necessary to follow the clinical course and to correlate it with the calculated dosage. The patient who received the smallest amount of radiation (the sublethal dose—about 400 rem) was given only the standard treatment (isolation, rest, diet, intensive vitamin therapy, adrenocortical and hepatic extracts, and amino acids, with antibiotics only in case of necessity); in the other 5 (4 who received lethal doses and 1 who received a supralethal dose), this treatment was supplemented by grafts of bone-marrow cells. The 4 patients who received lethal doses (600 to 1,000 rem) survived and are now in satisfactory condition, but the one who received the supralethal dose (about 1,000 rem) died of visceral complications on the 32nd day after the accidental irradiation, although the hematopoietic cell graft had already assured the restoration of his blood picture.

The clinical course of the patients followed that known to occur in acute total irradiation. An initial phase of radiologic shock was succeeded, first, by a 2-to-3-week period of latency, and then by a period of crisis extending over the 4th, 5th, and 6th weeks. The patients' general condition, which was comparatively good during the period of latency, deteriorated during the critical period, with significant attacks of fever during the 4th and 5th weeks, except in the case of the one who had received the smallest amount of radiation. A genuine typhoid state developed in the other 5; anorexia and nausea reappeared, and night sweats became profuse, while diuresis diminished. This alarming picture was responsible for the decision to try bone-marrow grafts in these patients. The 4 patients who survived began to improve after the grafts were given, but the improvement was complicated by episodes of disturbance due to visceral changes, so that their convalescence did not really begin until the third month.

The future course of the patients cannot easily be forecast. The possibility, in the immediate future, of secondary immunological reactions in the 4 survivors who received bone-marrow grafts cannot be excluded, because the differences in human and animal medullary tissue make it difficult to apply the results of animal experimentation to man. The short-term course, for a few months at least, will probably be marked by hematological fluctuations and spermatogenetic anomalies, as well as by the persistence of asthenia making a premature return to work inadvisable. One long-term result of the irradiation is probably an increased likelihood that leukemia and certain cancers will appear as time goes on. Expressions of opinion in regard to possible shortening of life at the present time would be premature.

Solitary Pulmonary Nodules Found in a Community-Wide Chest Roentgenographic Survey: A Five-Year Follow Up Study. S. M. Holin, R. E. Dwork, S. Glaser and others. Am. Rev. Tuberc. 79:427-439 (April) 1959 [New York].

A mass chest roentgenographic survey was conducted in Cleveland and Cuyahoga County, Ohio, from March to September, 1949, during which 673,218 screening films were taken, representing a coverage of almost 65% of the adult population. In 1954 the records and films of persons with abnormal findings were reviewed. From this group, 666 persons whose lesions met certain predetermined criteria were classified as having solitary pulmonary nodules and were selected for a 5-year follow-up study. All but 22 persons were traced. The over-all prevalence of solitary pulmonary nodules was 1 per 1,000 persons surveyed. Nodules were found more frequently in older persons, in males, and in whites. The etiology was established in only 13.8% of the study group. Only 3% of the nodules were proved to be malignant, and 9% were diagnosed as tuberculous. The larger nodules were much more frequently malignant than were the smaller ones, and not one of those with demonstrable calcification was found to be malignant. Of the total series, 80.5% of the persons were alive and had had no symptoms attributable to the nodule during the 5-year follow-up study. Only 2.6% of the study group had died of

causes related to the nodule, all the deaths being attributed to pulmonary malignancy. A total of 61 persons had died, whereas on the basis of the mortality rate in Cuyahoga County only 52 deaths were expected. The increase in the death rate was entirely attributable to pulmonary malignancy.

This study shows that the proportion of cancer in a group of persons with solitary pulmonary nodules will vary considerably according to the criteria used in selecting the group to be investigated. While the proportion of malignancies in the total of this series was only 3%, it was 35% in men of 45 years and over, with nodules showing no evidence of calcification, poorly circumscribed, and measuring 40 mm. or more in diameter. The decision for surgical removal of solitary pulmonary nodules should be highly individualized in each case, because the risk of malignancy does not seem clear enough to warrant excision as a routine procedure.

Leukaemia Following Irradiation in Utero. A. G. S. Cooper and A. W. Steinbeck. Brit. J. Radiol. 32: 265-268 (April) 1959 [London].

After citing previous reports on the causal association between irradiation and leukemia, the authors present the history of a 3-year-old girl who had been well until 2 weeks prior to admission; thereafter she became acutely tired and pale and bruised easily. The pediatrician found only small lymph nodes in most areas, a moderately enlarged liver, and a grossly enlarged spleen. There were signs of anemia, and the study of the white blood cell picture revealed leukemia. Despite repeated blood transfusions the patient died within 3 months of the first symptoms of leukemia. This child had received irradiation in utero during irradiation of an enlarged maternal spleen in the 4th month of pregnancy; 3½ years later the first signs of acute leukemia were obvious. The leukemia appeared to be an undifferentiated blast-cell type, an uncommon form after irradiation. However, it seems reasonable to accept a causal relationship in this instance in view of the latent period and the dose which was greater than that normally received during pelvimetry in pregnancy—a suggested causal association with leukemia in the child.

PUBLIC HEALTH

Simultaneous Use of Serum and Toxoid in Prophylaxis of Tetanus. L. Eckmann. Schweiz. med. Wchnschr. 89:311-315 (March 21) 1959 (In German) [Basel, Switzerland].

The author cites reports indicating disagreement and confusion with regard to the simultaneous use of tetanus serum and toxoid, and since simultaneous prophylaxis has been in use at the surgical clinic and the polyclinic of the University of Basel, an investigation was undertaken to ascertain the immunological results of the simultaneous use of serum and toxoid. Answers were sought to the following questions: 1. How does serum-toxoid prophylaxis compare with exclusive serum prophylaxis with regard to intensity and duration of passive immunity? 2. How does active immunization with exclusive use of toxoid compare with active immunization in serum–toxoid prophylaxis with regard to (*a*) intensity, (*b*) onset, (*c*) duration, and (*d*) later reactivation by means of booster doses of toxoid? In all, about 3,000 determinations of antitoxin values were carried out on about 700 patients.

Studies were made on 3 groups of patients. Those in the first group were concerned with determining immunity against tetanus in persons who had been subjected to serum-toxoid prophylaxis under various conditions from 1 to 6 years before; not only was the existing antitoxin content determined, but also the change that took place after a booster dose of toxoid. Special attention was given to persons in whom the original simultaneous prophylaxis had been incomplete, that is, they had received only the first toxoid injection together with the serum injection, but not the second or later injections. The demonstration of a booster effect, that is, a rapid increase in antitoxin titer after a new injection of toxoid, demonstrated that the earlier injection of toxoid was effective despite the simultaneous administration of serum. The author feels that this represents a conclusive answer to the question of mutual inhibition of serum and toxoid. This group also included patients who earlier had been subjected to serum-toxoid prophylaxis and who in the meantime had received a booster dose.

The second group of patients comprised those who had been subjected to serum-toxoid prophylaxis with various time intervals between individual injections and with varying doses of serum and toxoid. Those in the third group were controls, in that they had received only serum or only toxoid for active immunization; they were investigated for comparative antitoxin values. The findings demonstrated that active immunization is not suppressed by the simultaneous administration of serum in customary doses. An outline is given for tetanus prophylaxis in injured persons. In view of the complex immunological conditions, oversimplification is not advisable, but prophylactic measures must be adjusted to the differing individual conditions. For active immunization alone as well as for combined prophylaxis, 3 doses of toxoid should be administered, whether native, adsorbed, or precipitated toxoid is used. The interval between the first 2 toxoid injections may be as short as 3 weeks; however, 5 weeks have proved to be preferable. The third dose should follow 3 months later. The administration of antitoxin without toxoid is to be rejected. All prophylactic measures against tetanus should tend towards active immunization.

BOOK REVIEWS

Total Surgical Management. By James D. Hardy, M.S., M.D., F.A.C.S., Professor and Chairman, Department of Surgery, University of Mississippi Medical Center, Jackson. Modern surgical monographs. Editor in chief: I. S. Ravdin, M.D. Consulting editor: Richard H. Orr, M.D. Cloth. $9.50. Pp. 392, with 50 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 15/16 Queen St., Mayfair, London, W. 1., England, 1959.

This book deals entirely with treatment—preoperative, operative, and postoperative. It first takes up the general measures of preoperative and postoperative care; next specific operations are considered; and finally the more general postoperative sequellae are discussed. It is gratifying to note that the taking of his history and physical examination are given their proper emphasis as opposed to the practice of rushing the patient to the laboratory for a battery of tests. The importance and evaluation of biological age and pulmocardiorenal function are stressed. Five of the 24 chapters are devoted to fluid therapy and nutrition, blood replacement and shock, the management of wounds, preoperative and postoperative orders, and the management of burns. Individual operations are also discussed. Although this book is intended for the general surgeon it should also be valuable to interns, surgical residents, and qualified surgeons.

Trigeminal Neuralgia: Its History and Treatment. By Byron Stookey, A.M., M.D., Professor Emeritus of Clinical Neurological Surgery, and Joseph Ransohoff, M.D., Assistant Professor of Clinical Neurological Surgery, College of Physicians and Surgeons, Columbia University, New York. Cloth. $10.75. Pp. 366, with 86 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This monograph is based on over 700 cases of trigeminal neuralgia which were seen and operated on by Dr. Stookey, who also accepts the responsibility for the opinions expressed in this study. The chapters on nonsurgical treatment, alcohol injection, and the statistical studies were prepared by Dr. Ransohoff. The book is most complete. It begins with an interesting historical survey and proceeds to an analysis of the embryology, anatomy, and physiology of the trigeminal nerve. The manifestations of the disease and the differential diagnosis are next considered. Nonsurgical treatment of the condition as well as injection of alcohol and operations on the peripheral divisions of the nerve, the root proximal to the gasserian ganglion in the posterior fossa, and the spinal root of the trigeminal nerve in the medulla oblongata all receive full consideration. The authors believe that the only satisfactory treatment of the disease is section of the nerve immediately proximal to the ganglion, by means of a temporal approach. The operative technique and possible complications are fully covered. One of Dr. Stookey's recent contributions to the treatment of trigeminal neuralgia is that of dealing with the unusual cases of bilateral involvement. Here again he has shown how these cases are best treated by selective section of the posterior root fibers.

The authors have pointed out that the cause of this condition is unknown and that, although it is possible to relieve these patients of their intense suffering, a completely satisfactory treatment of this disease is not yet available. It is to be hoped that in the near future this disease will be better understood and that with added knowledge will come the possibility of treating this condition without operation, or at least without producing an anesthesia of the face. Unfortunately, as the authors have shown, none of the procedures now designed to achieve that end is entirely satisfactory. There is an extensive bibliography and a satisfactory index. The book is highly recommended to everyone interested in this subject. Although it has been prepared by two neurosurgeons, all physicians and surgeons should find it of value in understanding trigeminal neuralgia and in advising their patients.

Differentialdiagnose innerer Krankheiten: Eine kurzgefasste Darstellung für Ärzte und Studierende. Von Dr. Robert Hegglin, o. Professor für innere Medizin an der Universität Zurich. Sixth edition. Cloth. 79.50 marks; $18.85. Pp. 819, with 517 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

This handsome handbook has an impressive record of professional acceptance. Since 1952 it has gone through five previous editions and has been translated into Spanish and Italian. The third revision of the latter is now in preparation. The reasons for this success are clear as soon as one scans the first few pages. Not only is it a splendid example of printing and of the reproduction of medical illustrations but the text is distinguished by thoroughly modern viewpoints as well as by lucidity of style.

The feat of covering so vast a field as internal medicine in something less than 800 pages is accomplished by an excellent scheme of organization. After a section on general considerations pertaining to differential diagnosis, such as the causes of er-

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

ror, the influence of weather, age, sex, geography, race, and occupation, the author discusses the diagnostic possibilities in each of the following symptom groups: anemias, hemorrhagic diathesis, febrile states, headache, dyspnea, cyanosis, hypertension, chest pain, lung shadows, abdominal pain, diarrhea, obstipation, icterus, edema, kidney diseases, paralysis of voluntary movement, and loss of consciousness. References to the literature are up to date and carefully selected, and they cover the work of English and American, as well as German, French, and Italian, authors.

The section on thoracic pain not only includes angina pectoris and myocardial infarction but also stresses functional heart disorders and musculoskeletal sources of painful sensations. The discussion of hiatal hernia is especially well done. The subject of coronary insufficiency and thrombosis is well illustrated by electrocardiograms. Throughout the work the diagnostic value of laboratory procedures is emphasized, without in any way belittling the clinical judgment of the physician.

This work is highly recommended to students and physicians with a good reading knowledge of German. Even for the casual reader, less gifted linguistically, study of the pictures will be worthwhile.

Surgery of the Prostate. By Henry M. Weyrauch, M.D., F.A.C.S., Clinical Professor of Surgery (Urology); Chief, Division of Urology, Stanford University School of Medicine, San Francisco. Cloth. $15. Pp. 535, with 288 illustrations by Halcyon Harris Cowles and Ralph Sweet. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

In the past 40 years surgery of the prostate has been marked by revolutionary advances. One has only to compare present-day monographs which depict modern methods accompanied by an insignificant mortality and morbidity with the early publications of Fuller, Guiteras, Belfield, and others in America or the works of Freyer or Thomson-Walker in England, at which time the operative mortality for prostatectomy averaged 25 to 30%, to realize how great these advances have been. The extensive monograph here reviewed is an admirable guide to all the accepted procedures associated with the treatment of bladder neck obstruction in men. This well-illustrated book presents surgical technique in great detail. Surgical anatomy and pathology are briefly reviewed, and the diagnosis of prostatic obstruction and the indications for its surgical correction are well covered. The historical summary is not all-inclusive, but for this type of text it is adequate. All the present-day surgical approaches to the problem of relieving prostatic obstruction are described and illustrated in great detail. There are statements in the chapter on preoperative care and treatment that are not universally accepted by urologists, but in the main these are of no great importance. The training of the surgeon is rightly emphasized. This monograph can be highly recommended for all who plan to treat diseases of the prostate by surgical means.

Advances in Virus Research. Volume VI. Edited by Kenneth M. Smith and Max A. Lauffer. Cloth. $10. Pp. 382, with illustrations. Academic Press, Inc., 111 Fifth Ave., New York 3, 1959.

At least five of the seven comprehensive and technical reviews included in this volume are unrelated to medical practice. They deal with the purification, biochemistry, and spread of plant viruses; one deals with bacteriophage genetics and another with paramecium. The other two are concerned with medical topics, but at a highly technical level that will interest only the virologist. One reviews the purification and properties of poliovirus and is especially concerned with the nature of formalin inactivation of the virus. The evidence for and against this being a reaction of the first order is carefully reviewed. The physical, chemical, and serologic properties of poliovirus are thoroughly presented. The other review is limited to a consideration of the present knowledge of the measles virus. This includes its behavior in tissue culture, growth characteristics, size, serologic reactions, and relation to the distemper virus. The prospects for a killed vaccine in the near future are discussed. The reviews presented in this book are comprehensive, authoritative, and supported by a full bibliography. The subject matter, however, limits the appeal to plant and animal virologists.

Surgery of the Ear. By George E. Shambaugh, Jr., M.D., Professor of Otolaryngology, Northwestern University Medical School, Chicago. Cloth. $27.50. Pp. 669, with 326 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

This massive book has quality as well as quantity. One may not be able to learn otology from pictures in a book, but, if one could, here are the pictures and the descriptive text to go along with them. More than 30 years have passed since anything like it has appeared in this field. It is dedicated to the memory of Gunnar Holmgren, whose death in 1954 left a void among the limited number of researchers in otology. It is Holmgren who, together with Prof. Barry Anson, did such an amazing amount of laboratory work on the anatomy of the ear. Part 1 describes this enterprise in detail. Part 2 is devoted to surgery of infections of the ear, part 3 to surgery of deafness, and part 4 to surgery of the facial nerve, endolymphatic hydrops, and tumors of the ear. At the end of each chapter is an exhaustive list of references. The final pages are given to an index of names and a subject index. This work is so monumental that it is not possible to do it justice in a short space. As an example of the best in bookmaking it is superb as to paper, print, and general format.

QUESTIONS AND ANSWERS

ATRIAL FIBRILLATION

To the Editor:—*If a 70-year-old patient has irregular irregularity, with an apical rate of 120 and a radial rate of 100 per minute, may one assume he has auricular fibrillation? Without an electrocardiogram, would it be safe to attempt conversion of this type of arrhythmia with quinidine if it were known to have been present for short periods in the recent past? If one used quinidine, should one digitalize the patient first? What are the various causes of a pulse deficit?*

Burdge F. Green, M.D., Stilwell, Okla.

Answer.—The evidence suggests atrial (auricular) fibrillation as the most probable diagnosis. Apparent "irregular irregularity" of an arterial pulse may be detected in cases of atrial tachycardia or flutter, with a rapidly and randomly varying grade of second-degree atrioventricular block in which, in quick and disorderly succession, the block may go from 2:1, to 3:1, to 3:2, to 4:1, etc.; but this, compared with atrial fibrillation, is less common. Fairly often, a normal sinus rhythm with frequent atrial or ventricular premature contractions, or a marked sinus arrhythmia, will produce an irregularity of rhythm that superficially mimics atrial fibrillation. Assuming the problem under consideration does represent atrial fibrillation, and providing symptoms and signs of heart failure are absent (the presence of heart failure demands the use of digitalis), it would seem safe to attempt a cautious conversion with quinidine. It must be noted, however, that in this situation, even without heart failure, many cardiologists would use digitalis, usually one of the rapidly acting glycosides, in an attempt to cause reversion to a normal sinus mechanism. In the absence of decompensation, one need not digitalize that patient before giving quinidine. The possibility of a so-called masked hyperthyroidism ought to be kept in mind in cases of this type, as should mediastinal disease; these conditions are occasionally attended with atrial fibrillation.

A pulse deficit is simply one peripheral manifestation of intermittent reductions in the left ventricular stroke volume that occur as a result of a shortened diastole with resulting insufficient time for ventricular filling; it may be detected, therefore, whenever one beat, out of phase, follows another in close succession, as may happen whenever premature ventricular or supraventricular contractions occur, or during atrial fibrillation. The importance of electrocardiographic observations, both in the diagnosis of arrhythmias and as aids in monitoring the response to quinidine, must be emphasized.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

DETERGENT FOR INTESTINAL TUBE LAVAGE

To the Editor:—*Might toxic effects be produced if 5 cc. of the commercial detergent Vel were diluted with 25 cc. of saline solution, passed through a Miller-Abbott tube to about the mid-ileum, allowed to remain for 15 minutes, and then withdrawn by suction? Recently, in a patient with intestinal obstruction, the Miller-Abbott tube clogged constantly. Use of the above procedure twice daily for three days kept it functioning satisfactorily.*

Paul J. Laube, M.D., Dubuque, Iowa.

Answer.—Vel is a solution of alkyl benzene sulfonate (30%) and sodium sulfate (70%) in denatured ethyl alcohol (0.4%). There is no clinical or experimental evidence that any of these might have toxic effects when employed in the manner indicated. Withdrawal after 15 minutes would make any such possibility still more unlikely.

"S. O. S." VERSUS "P. R. N."

To the Editor:—*I have stirred up a tempest in a teapot in a local hospital and need a learned opinion to save my face. The controversy arose when a nurse asked why I wrote orders sometimes followed by "s. o. s." and at other times by "p. r. n.," when they apparently meant the same thing. I explained that s. o. s. applied to a one-time order, while p. r. n. anticipated the need for repetition. The situation has burgeoned into a* cause célèbre, *with most old-timers on my side and most young folks against me. I will appreciate an opinion.*

Aaron Merker, M.D., Bronx, N. Y.

Answer.—As is so often true in teapot tempests and minor polemics, the issue is not exact enough for an absolute answer to be given. The Latin words for which the initials p. r. n. stand are *pro re nata*, generally translated "as occasion requires" or "as need occurs." This implies the possibility of repetition of a dose or a special procedure. The initials s. o. s. stand for *si opus sit*, a subjunctive clause which is freely translated "if necessary" or "if the need or work should be or exist." As Latin expressions, both have about the same implication. Both

admit repetition, though s. o. s. is not as strong in the idea of recurring necessity. On the other hand, common usage sides with the beleaguered physician from the Bronx. Custom supports his traditional approach even though a literal translation of the two Latin expressions does not establish strong support for the difference in these expressions as customarily used. One can take comfort or despair from the fact that meaning changes and words are fickle. Constant use, even misuse, eventually establishes acceptance, so that wrong becomes right in the curious democracy of words. This is true of pronunciation as well as definitions, and horrified grammarians can no more stem the tide than Canute could sweep back the ocean. The contest is a draw.

CIGARETTE HABIT

To the Editor:—*What is the name of the nasal spray or medicine that can be taken orally that is useful in stopping the cigarette habit?*

G. Howard Wood, M.D., Chillicothe, Ohio.

Answer.—Over some years, alpha-lobeline has been used as a smoking deterrent. However, there is little agreement as to the results. Wright and Littauer (*J. A. M. A.* **109**:649-654 [Aug. 28] 1937) found that it was an effective smoking deterrent in capsules of 8 mg., but the side-reactions, such as gastric distress, vomiting, and circulatory effects, were too drastic to permit use. Rapp and Olen (*Am. J. M. Sc.* **230**:9, 1955) used a tablet which contained only 2 mg. of lobeline with at least a 100 mg. mixture of slow-acting and fast-acting antacids. This they reported to have a safe and deterrent effect on smoking, particularly if the patient wished to stop. In contrast, when Bartlett and Whitehead (*J. Lab. & Clin. Med.* **50**:278, 1957) compared the effectiveness of this tablet with meprobamate and a sugar placebo, the lobeline and meprobamate were no more effective than the placebo.

IRRADIATION OF THYMUS

To the Editor:—*Please indicate the consensus regarding radiation of an enlarged thymus gland.*

Prentiss M. Kinney, M.D., Bennettsville, S. C.

Answer.—If the case is one of malignant thymic involvement, radiation is indicated, useful, and worthwhile, and its employment is proper. When thymic involvement is benign, which is the case in the majority of instances, a conservative attitude must be considered with respect to irradiation. Whereas there is no record of an increase in the rate of malignancy of the thyroid in adults after even persistent radiation of the neck, and while radiation has been used effectively for treatment of an enlarged thymus that may be causing oppressive symptoms in children, not all pediatricians are in accord with its employment in such cases. Although the number of instances is small, the possibility of thyroid malignancy developing subsequent to irradiation of the head, neck, and thorax during infancy and childhood might be borne in mind. Simpson and Hempelmann (*Cancer* **10**:42, 1957) found 10 cases in 1,502 children treated for enlarged thymus. However, among 1,933 untreated persons they found 5 who developed carcinoma. Roone and Powell (*J. A. M. A.* **169**:1-4 [Jan. 3] 1959) record the finding of 10 patients, including 2 of their own, in Georgia, who developed thyroid malignancy and who had a history of having had irradiation during infancy and childhood. During an experience of 30 years in a large general public hospital, this consultant has used irradiation for many thymic conditions that were producing obstructive symptoms in children and has not noted any case of thyroid carcinoma developing subsequently during a follow-up of many years. Radiation when used must be administered properly and with correct dosage over as short a period of time as required by the exigencies of the case.

PENICILLIN ABSORPTION RATES

To the Editor:—*Please give duration of action of benzathine penicillin G, procaine penicillin in oil, and procaine penicillin G in aqueous suspension.*

Aubrey L. Shelton, M.D., Norfolk, Va.

Answer.—The average duration of action of benzathine penicillin G is approximately four weeks. The average duration of action of procaine penicillin in oil and procaine penicillin G in aqueous suspension is 24 to 48 hours. Since there is little or no difference in the duration of action of these two, the latter is preferred because procaine penicillin in oil on occasion may result in oil cysts at the site of injection.

ACTION OF PHYSOSTIGMINE

To the Editor:—*What specific action does physostigmine possess that results in the onset of delayed menstruation? I am aware of the anticholinesterase action of physostigmine, resulting in a temporary cholinergic excess. Is the onset of menstruation related to this cholinergic excess, and is epinephrine called into action by this excess? If either is so, what relationship exists with estrogens?*

G. H. Reye, M.D., Sedro Woolley, Wash.

Answer.—Neostigmine, a compound chemically related to physostigmine, is generally used to induce menstruation in functional amenorrhea. The idea of using neostigmine had its origin when Reynolds and Foster (*Am. J. Physiol.* **127**:343, 1939) reported hyperemia and increased acetylcholine in the rat uterus after estrogen therapy. The estrous phenomenon in animals is partly dependent on the uterine hyperemia, apart from the specific proliferative changes caused by estrogen. It seems that a similar relationship exists in humans between the uterine hyperemia and cyclic menstrual bleeding. The mechanism of hyperemia presumably is under the influence of the parasympathetic nervous

system. Here again, in "functional" or "nervous" amenorrhea, in the absence of any organic dysfunction, it seems possible that the amenorrhea is due to decreased vascular responsiveness of the uterus. The cholinergic-like action of estrogen and the bleeding presumably induced by neostigmine are analogous, and this appears to be negated by the presence of progesterone (Soskin, S.; Wachtel, H.; and Hechter, O.: *J. A. M. A.* 114:2090-2091 [May 25] 1940). The role of epinephrine in influencing neostigmine bleeding is not clearly known.

TREATMENT OF HYPERHIDROSIS

To the Editor:—*Considering the great advances in drugs affecting the parasympathetic nervous system, are there any new developments in treatment of hyperhidrosis?*

J. S. Newton, M.D., Lewiston, Idaho.

Answer.—There are no new developments in the treatment of hyperhidrosis by drugs affecting the parasympathetic nervous system. Since the introduction of methantheline and propantheline, these and other anticholinergic drugs have been used in the treatment of hyperhidrosis. Some patients are benefited, but the effect is not uniform, and many patients complain severely of the side-effects, such as dryness of the mouth and blurred vision. In an occasional patient, the therapeutic effect is gratifying.

CAUSE OF CHEILOSIS

To the Editor:—*A man, aged 76, in good physical condition, has developed cheilosis and angular stomatitis. He wears dentures, which he finds perfectly comfortable, is not on a restricted diet, and has been taking one tablet of an ascorbic acid and vitamin B complex supplement daily for the past 10 years. For the last two months he has been taking 2 to 3 tablespoonfuls of barley malt extract as a laxative. This preparation contains 0.05% butyl parahydroxybenzoate as a preservative. Could this be responsible for the cheilosis? Might the fact he has been taking both the laxative and the vitamin B supplement at breakfast be significant? I would greatly appreciate an opinion on the etiology of this case.*

M.D., New York.

Answer.—Not all the categories of causes of cheilosis or cheilitis are known. Of those best known are the type due to vitamin deficiency and that due to allergy. Vitamin deficiency should be ruled out in this case by using potent preparations. Allergic causes have been mainly of the contact type, although ingredients in foods are a possibility. Preservatives and other food additives have been particularly suspected in recent years to be the source of various types of allergy, and the chemical mentioned may fall into this category. If there are no clues as to contact allergy, a temporary (10 to 14 day) restricted diet may indicate whether any food allergy might be involved. Also to be considered is the fact that the aged skin—especially in the areas indicated, where it is subject to irritation from saliva—may be more prone to trophic changes and low-grade infection.

DIGITALIS AND PLACENTAL BARRIER

To the Editor:—*Does digitalis pass the placental barrier? If so, is it harmful to the fetal heart?*

Humberto Nunez Bossio, M.D.
Bogotá, Colombia.

Answer.—No evidence is known of any transfer of digitalis across the human placenta. Consideration of the structure and size of the digitalis molecule makes this highly unlikely. Many pregnant women have received digitalis, and no reports are known of harmful effects on the fetus or newborn infant.

TIETZE'S SYNDROME

To the Editor:—*A possible case of Tietze's syndrome has come to my attention (a nonsuppurating painful swelling of the costochondral junction of unknown etiology). Is there any treatment recommended? What is the prognosis?*

H. E. Pfeiffer, M.D., Riviera Beach, Fla.

Answer.—Pain and swelling of the costochondral cartilages often cause considerable anxiety which can be alleviated when the physician informs the patient that the condition is no indication of serious disorder. The most important treatment is therefore reassurance, hoping thereby to alleviate the psychoneurosis which so frequently accompanies this condition.

ESTROGENS AND CLOTTING

To the Editor:—*The questions related later are relevant to the history of a 68-year-old woman with coronary insufficiency of 20 years' duration. She was treated satisfactorily with nitroglycerin, in anticipation of effort, and niacin was prescribed to control hypercholesteremia (cholesterol level 315 mg. per 100 ml.). Intermittent claudication for the past two years has reduced her walking tolerance, but she experiences no cramps of her calf muscles during hours of activity. The bilateral absence of posterior tibial and dorsalis pedis pulsations was diagnosed as due to acute occlusion of the left lower extremity. This was found with the aid of oscillometry to be a complication of coronary artery disease. To treat persistent hypercholesteremia, orally given conjugated estrogens were prescribed for 30 days. After this, the cholesterol level was 259 mg. per 100 ml.*

The Question and Answer entitled "Estrogens and Clotting" which appeared in The Journal, *April 11, page 1811, was informative. The question referred to is, "If estrogens . . . control hemorrhage. . . . would there not be a greater*

possibility of arterial occlusion . . . ?" The consultant's answer was: "The continued oral administration . . . does not have the same effect" (presumably as intravenous injection). I believe that however mild the tendency might be toward coagulation by estrogen therapy, although orally administered, such therapy should be contraindicated in peripheral arterial occlusion. What is the medical opinion and on what basis do conjugated estrogens cause a lowering of the blood cholesterol level? Of niacin and conjugated estrogens, which should be the choice for continued administration?

Benjamin Erps, M.D.
1223 S.W. 11th Ave.
Miami, Fla.

The above comment has been referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*Alterations of coagulation occur with intravenous injections of conjugated estrogens in the relatively large dose of 20 mg. With intravenous administration of smaller amounts, less change is noted. Treatment of this type is for no longer than 24 hours. Continued administration of such a large amount would lead to the expected endocrinological changes in either sex, particularly objectionable in men. Smaller oral doses would have little effect on the coagulation components.*

The effect of estrogen administration on the cholesterol level is a coincidental reduction. With elevation of estrogen level during the menstrual cycle there is reduction in the circulating cholesterol and beta-lipoprotein cholesterol levels. With the menopause there is elevation of the cholesterol level as the estrogen level falls. Conversely, during pregnancy there is an elevation of the cholesterol level that chronologically parallels that of the estrogens. At the same time there is an elevation of the progesterone level and that of certain adrenal steroids and other hormones. It is not known whether the effects of the other hormones mask the changes coincident with estrogen rise or whether there are other mechanisms operating during the complex sequence of endocrinological interplay of pregnancy. The direct relationship between estrogens and cholesterol awaits further description.

A summary of relationships of estrogens and the lipids of the plasma can be found in an article by Oliver and Boyd (Hormonal Aspects of Coronary Disease, in Vitamins and Hormones: Advances in Research and Applications, edited by R. S. Harris, G. F. Marrian, and K. V. Thimann, vol. 16, New York, Academic Press, Inc., 1958, p. 147). In the same book there is an article by Felch and co-workers (Vitamins and Other Nutrients in Cardiovascular Disease) which mentions the relationship of niacin and the lipids of the plasma.

As to choice of preparations, I would favor niacin for long-term therapy. The choice would be based on the endocrinological aspects of continued estrogen therapy and not on the alterations of blood-clotting factors, because I do not believe that the changes would be of sufficient magnitude to be of concern.

RECURRENT PHLEBITIS

To the Editor:—*I was very much interested in the answer to a question concerning a patient who had recurrent phlebitis (The Journal, March 28, 1959, page 1541). Although, as the consultant states, apparently the original cause is not definitely known, I believe it should be stressed that a search should be made for malignancy. In spite of the long survival, it is still possible the patient may be suffering from an occult malignancy of the pancreas, ovary, lung, etc. I recently reviewed 102 cases in which phlebitis was the sole indication of visceral malignancy. My summary was published in* The Journal of the Kentucky State Medical Association (36:364, 1958).

William T. Rumage Jr., M.D.
523 Fincastle Bldg.
Louisville, Ky.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*In my original discussion of the query, the statement was made that the cause of the recurring episodes of thrombophlebitis was not known or, at least, was not clear, but I presumed it most likely had an infectious or traumatic background. In my experience, these are the most common etiological factors in such cases. Incidence may conservatively be estimated at about 75%. Malignancy is recognized as a possible contributory cause, both in thrombophlebitis and in arterial thrombosis. However, the incidence is low. In my opinion, it may occur in about 3 to 5% of the cases.*

It is true that when dealing with a patient with either recurring thrombophlebitis or arterial thrombosis, when the usual or more common etiological factors are not clear, one should keep in mind the possibility of malignancy. This is particularly true when dealing with a patient who has other symptoms and manifestations not related to the circulatory disorder. On such occasions, masked or unrecognized malignancy is mentioned for further investigation. In such a situation, diagnosis of malignancy usually is established within a period of three to six months. In this particular case, I cannot conceive of an unrecognized malignancy existing for five years without manifestations which would make the diagnosis of cancer apparent.

SUBJECT INDEX

The letters used to explain in which department the matter indexed appears are as follows: "E," Editorial; "C," Correspondence; "ab," abstracts; the asterisk (*) indicates an original article in THE JOURNAL. Page numbers in the index refer to the bold face numbers in the text.

This is a subject index and one should, therefore, look for the subject word with the following exceptions: Foundations, Lectures, Moving Pictures, and Prizes, under "F," "L," "M," and "P" respectively. "Book Reviews," "Deaths," "Medicolegal Abstracts" and "Societies" are indexed under these titles at the end of the letters "B," "D," "M," and "S." Matter pertaining to the Association is indexed under "American Medical Association." The name of the author, in brackets, follows the subject entry.

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Acad.—Academy
Am.—American
A.—Association
Coll.—College
Commn.—Commission
Comm.—Committee
Conf.—Conference
Cong.—Congress
Dist.—District
Div.—Division
Found.—Foundation
Hosp.—Hospital
Indust.—Industrial
Inst.—Institute
Internat.—International
M.—Medical
Med.—Medicine
Nat.—National
Pharm.—Pharmaceutical
Phys.—Physicians
Soc.—Society
Surg.—Surgery
Surgs.—Surgeons
S.—Surgical

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